KDIGO 2026 CLINICAL PRACTICE GUIDELINE FOR ACUTE KIDNEY INJURY (AKI)AND ACUTE KIDNEY DISEASE (AKD)

PUBLIC REVIEW DRAFT
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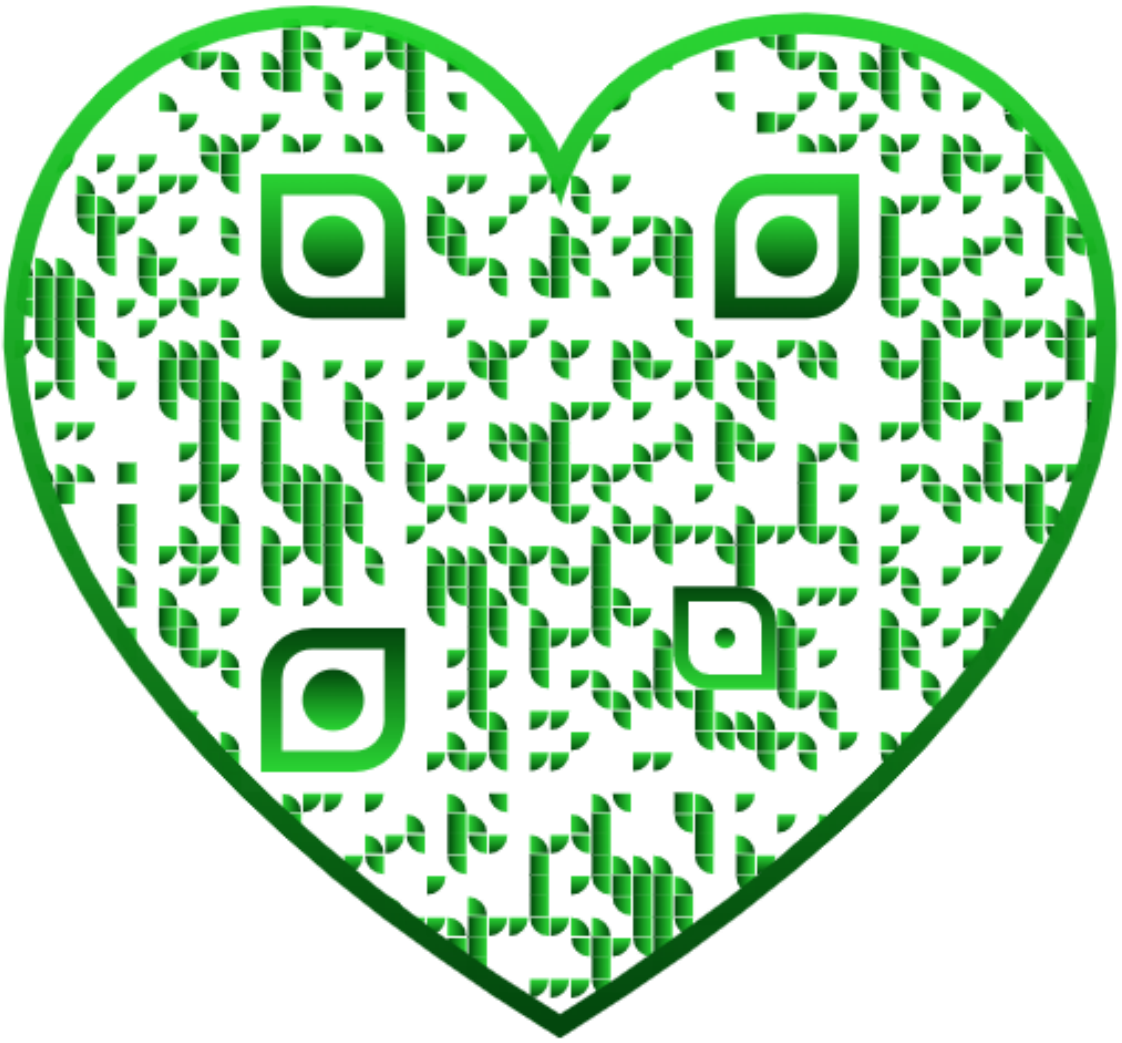

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ABBREVIATIONS AND ACRONYMS

AAMI	American Association of Medical Instrumentation
ACEi	angiotensin-converting enzyme inhibitor
ADQI	Acute Dialysis Quality Initiative
AIN	acute interstitial nephritis
AKD	acute kidney disease
AKI	acute kidney injury
AKIN	Acute Kidney Injury Network
ARB	angiotensin II receptor blocker
ATI	acute tubular injury
ATN	acute tubular necrosis
AUROC	area under the receiver operating characteristic curve
AUC	area under the curve
BMI	body mass index
BP	blood pressure
CA-AKI	contrast-associated acute kidney injury
CDSS	clinical decision support system
CI	confidence interval
CKD	chronic kidney disease
CRRT	continuous renal replacement therapy
CVVHD	continuous venovenous hemodialysis
CVVHDF	continuous venovenous hemodiafiltration
ECLS	extracorporeal life support
eGFR	estimated glomerular filtration rate
EHR	electronic health record
ERT	Evidence Review Team
FDA	Food and Drug Administration
GLP-1 RA	glucagon-like peptide-1 receptor agonist
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GFR	glomerular filtration rate
HD	hemodialysis
HR	hazard ratio
HRQoL	health-related quality of life
HVHF	high-volume hemofiltration
ICU	intensive care unit
IHD	intermittent hemodialysis
IRRT	intermittent renal replacement therapy
ISPD	International Society of Peritoneal Dialysis
KDIGO	Kidney Disease: Improving Global Outcomes
KeGFR	kinetic glomerular filtration rate
KTR	kidney transplant recipient
MAKE	major adverse kidney events
MAP	mean arterial pressure
MCV	mean corpuscular volume
MD	mean difference
MRA	mineralocorticoid receptor antagonist
NSAID	nonsteroidal anti-inflammatory drugs

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OR	odds ration
QoL	quality of life
PD	peritoneal dialysis
PICOS	population, intervention, comparator, outcomes, and study design
PICU	pediatric intensive care unit
PIRRT	prolonged intermittent renal replacement therapy
RAI	Renal Angina Index
RASi	renin-angiotensin system inhibitor
RCT	randomized controlled trial
RD	risk difference
RIFLE	Risk, Injury, Failure; Loss, End-Stage Renal Disease
RR	risk ratio
RRT	renal replacement therapy
SCr	serum creatinine
SD	standard deviation
SGLT2i	sodium-glucose co-transporter-2 inhibitor(s)
UACR	urine albumin-to-creatinine ratio
UFH	unfractionated heparin
U.S.	United States
USRDS	United States Renal Data System
WHO	World Health Organization

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NOTICE

SECTION I: USE OF THE CLINICAL PRACTICE GUIDELINE

This Clinical Practice Guideline document is based upon literature searches last conducted in June 2025. It is designed to assist decision-making. It is not intended to define a standard of care and should not be interpreted as prescribing an exclusive course of management. Variations in practice will inevitably and appropriately occur when clinicians consider the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Healthcare professionals using these recommendations should decide how to apply them to their own clinical practice.

SECTION II: DISCLOSURE

Kidney Disease: Improving Global Outcomes (KDIGO) makes every effort to avoid any actual or reasonably perceived conflicts of interest that may arise from an outside relationship or a personal, professional, or business interest of a member of the Work Group. All members of the Work Group are required to complete, sign, and submit a disclosure and attestation form showing all such relationships that might be perceived as or are actual conflicts of interest. This document is updated annually, and information is adjusted accordingly. All reported information is published in its entirety at the end of this document in the Work Group members' Disclosure section and is kept on file at KDIGO.

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WORK GROUP MEMBERSHIP

Work Group Co-Chairs

Marlies Ostermann, PhD, MD
Guy's & St Thomas' Hospital
London, UK

Matthew James, MD, PhD
University of Calgary
Calgary, Alberta, Canada

The Work Group consisted of a geographically diverse group of experts including the following specialties: adult and pediatric nephrology, critical care medicine, emergency medicine, general medicine, pharmacy and pharmacology, as well as people with lived experience of AKI.

Methods Committee Representative

Gihad Nesrallah, MD, MSc, FRCPC, MBA
University of Toronto
Toronto, Ontario, Canada

Jitendra Meena, MD, DM
All India Institute of Medical Sciences,
New Delhi, Delhi, India

Evidence Review Team

Center for Evidence Synthesis in Health, Brown University School of Public Health, Providence, Rhode Island, USA

Ethan M. Balk, MD, MPH, Project Director, Evidence Review Team Director
Craig E. Gordon, MD, MS, Assistant Project Director, Evidence Review Team Associate Director; Professor of Medicine, Division of Nephrology, Tufts University School of Medicine, Tufts University School of Medicine
Gaelen P. Adam, MLIS, MPH, PhD, Senior Research Associate, Information Specialist

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ABSTRACT

The Kidney Disease: Improving Global Outcomes (KDIGO) 2026 Clinical Practice Guideline for Acute Kidney Injury (AKI) and Acute Kidney Disease (AKD) is an update of the KDIGO 2012 guideline on the topic. The guideline informs the care of adults and children at risk for or with AKI and AKD. The guideline includes chapters dedicated to AKI and AKD definition, identification, and classification; AKI prediction, risk stratification, and diagnostic evaluation; prevention and treatment of AKI, drug- and nephrotoxin-associated AKI; renal replacement therapy; and follow-up care after AKI or AKD. The update considers evidence from studies published through June 2025. The guideline provides actionable recommendations based on a rigorous formal evidence review, practice points that were not based on a systematic review and supporting infographics. The target audiences for the guideline are healthcare professionals involved in the care of people with AKI or AKD as well as people with or after resolution of AKI themselves. Development of the guideline followed an explicit process of evidence review and appraisal. The guideline recommendations are based on systematic reviews of relevant studies, and appraisal of the certainty of evidence and of the strength of recommendations following the "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) approach. Limitations of the evidence are discussed and suggested areas for future research are also presented.

Keywords: acute kidney disease, acute kidney injury, evidence-based; guideline; KDIGO; systematic review; GRADE

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SUMMARY OF RECOMMENDATION STATEMENTS AND PRACTICE POINTS

CHAPTER 1. AKI AND AKD DEFINITION, IDENTIFICATION, AND CLASSIFICATION

1.1. Definition of AKI

Practice Point 1.1.1: Acute kidney injury (AKI) in children and adults is defined by the presence of one or more abnormalities of kidney function or structure known or presumed to have occurred within 7 days, in the appropriate clinical context (Table 1).

Table 1 | Criteria for acute kidney injury for children and adults (any one or more of the following within the corresponding time period)

Functional criteria	Structural criteria
• Increase in SCr by ≥0.3 mg/dl (≥26.5 μmol/l) within 48 hours • Increase in SCr by ≥1.5 times baseline that is known or presumed to have occurred within the prior 7 days • Increase in serum cystatin C by ≥1.5 times baseline that is known or presumed to have occurred within the prior 7 days • Mean urine volume of less than 0.5 ml/kg/h (based on ideal body weight) for ≥6 hours	• Elevation of a biomarker of kidney damage when used for its clinically validated and regulatory qualified indication, which is known or presumed to have occurred within the prior 7 days

SCr, serum creatinine

Recommendation 1.1.1: We suggest using serum cystatin C to identify AKI in children and adults in clinical situations when serum creatinine (SCr) is less accurate *(2B)*.

Practice Point 1.1.2: A baseline SCr value should be ascertained for all patients with suspected or confirmed AKI.

Practice Point 1.1.3: In adults, select the baseline SCr or cystatin C for an AKI episode using a hierarchical approach (Figure 1).

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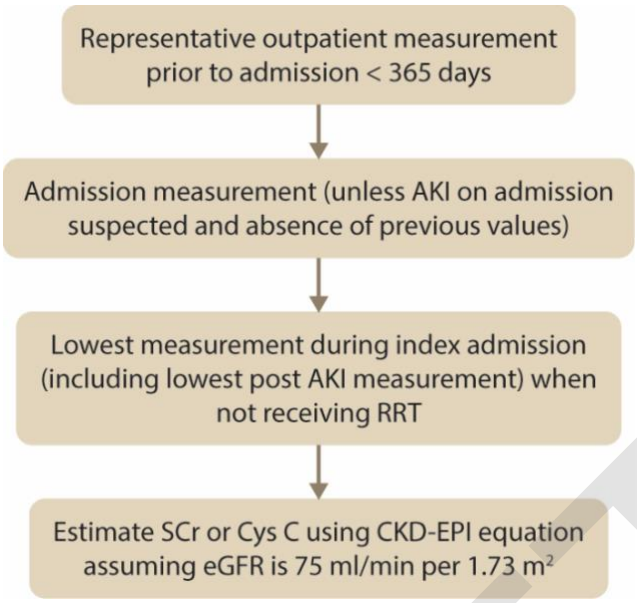
Representative outpatient measurement prior to admission < 365 days
Admission measurement (unless AKI on admission suspected and absence of previous values)
Lowest measurement during index admission (including lowest post AKI measurement) when not receiving RRT
Estimate SCr or Cys C using CKD-EPI equation assuming eGFR is 75 ml/min per 1.73 m²

Figure 1 | Hierarchical approach to the selection of the baseline SCr value used to characterize an AKI event in adults*. *A representative primary care/outpatient serum creatinine (SCr) should ideally reflect the stable clinical state, and may be a mean, median, or most recent value between 8–365 days before a hospital admission (or acute event). AKI, acute kidney injury; Cys C, cystatin C; eGFR, estimated glomerular filtration rate; RRT, renal replacement therapy

1.2. Staging of AKI

Practice Point 1.2.1: The severity of AKI in children and adults is staged according to individual components or combinations of the following SCr and urine output criteria and presence or absence of an elevated biomarker of kidney stress or damage (Table 6).

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Table 6 | Severity staging system for AKI

Functional criteria				Structural criteria	
Serum creatinine		Urine output		Damage biomarker	
Stage	**Criteria**	**Stage**	**Criteria**	**Stage**	**Criteria**
C0		**U0**		**B1**	**Positive**
C1	≥0.3 mg/dl (≥26.5 µmol/l) increase, *Or* 1.5-1.9 times baseline	**U1**	<0.5 ml/kg/h for 6–12 hours	**B0**	Negative
				B1	Positive
C2	2–2.9 times baseline	**U2**	<0.5 ml/kg/h for >12 hours	**B0**	Negative
				B1	Positive
C3	≥3.0 times baseline, *Or* Increase in SCr to ≥4.0 mg/dl (≥353.6 µmol/l) *Or* Initiation of RRT	**U3**	<0.3 ml/kg/h for >24 hours or anuria for >12 hours	**B0**	Negative
				B1	Positive

*C1-C3 indicates acute kidney injury (AKI) severity stage according to serum creatinine (SCr) criteria, U1-U3 indicates AKI severity stage according to urine output criteria, B0/B1 indicates staging by absence or presence of an elevated damage biomarker. Relevant components of the staging system can be employed to classify the severity of AKI according to the measurements collected for an individual. RRT, renal replacement therapy

Practice Point 1.2.2: Transient AKI is differentiated from persistent AKI based on an increase in SCr or cystatin C or decrease in urine output lasting ≤48 versus >48 hours (Table 7).

Table 7 | Definitions of transient and persistent AKI

	Duration of reduction in kidney function
Transient AKI	≤48 hour increase in SCr or cystatin C or reduced urine output
Persistent AKI	>48 hour and up to 7 days increase in SCr or cystatin C or reduced urine output

AKI, acute kidney injury; SCr, serum creatinine

Practice Point 1.2.3: The underlying cause of AKI should be identified based on susceptibilities and exposures, clinical context, history and physical examination, and appropriate diagnostic laboratory and imaging testing to inform specific management.

1.3. Definition of AKD

Practice Point 1.3.1: Acute kidney disease (AKD) in children and adults is defined as the presence of any of the following functional or structural criteria in the appropriate clinical context with a duration ≤3 months (Table 9).

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Table 9 | Criteria for AKD (any one or more of the following with a duration ≤3 months)

Functional criteria	Structural criteria
AKI (by functional criteria), *Or* GFR <60 ml/min per 1.73 m^2* *Or* Decrease in GFR by ≥35 ml/min per 1.73 m^2 from baseline *Or* Increase in SCr by >50%	AKI (by structural criteria) *Or* Marker of kidney damage (albuminuria, hematuria, or leukocyturia are most common)

*GFR <60 ml/min per 1.73 m^2 criterion does not apply to children younger than 2 years old. AKI, acute kidney disease; AKI, acute kidney injury; GFR, glomerular filtration rate; SCr, serum creatinine

Practice Point 1.3.2: AKD without AKI should be differentiated from AKD following AKI because the underlying causes and clinical management can be different.

1.4. AKI and AKD resolution

Practice Point 1.4.1: Complete and partial resolution of AKI and AKD are defined by changes in SCr, serum cystatin C, or estimated glomerular filtration rate (eGFR) as shown in Table 10.

Table 10 | Criteria for resolution of AKI and AKD

	Complete resolution	Partial resolution
AKI	SCr or serum cystatin C <1.2 times higher than baseline within 7 days	SCr or serum cystatin C ≥1.2 to <1.5 times higher than baseline within 7 days
AKD	SCr or serum cystatin C <1.2 times higher than baseline, *Or* eGFR ≥80% of baseline within 3 months	SCr or serum cystatin C ≥1.2 to <1.5 times higher than baseline, *Or* eGFR <80% to >66% of baseline within 3 months

AKD, acute kidney disease; AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; SCr, serum creatinine

1.5. Recurrent AKI

Practice Point 1.5.1: Recurrent AKI is defined as a new episode of AKI occurring after partial or complete resolution from a previous episode of AKI.

1.6. Considerations specific to children

1.6.1. Definition of AKI

Practice Point 1.6.1.1: Age specific references ranges should be used when serum cystatin C is used to detect AKI in children

1.6.2. Determination of baseline kidney function

Practice Point 1.6.2.1: In children (except neonates), select the baseline SCr or serum cystatin C for an AKI episode using a hierarchical approach (Figure 3).

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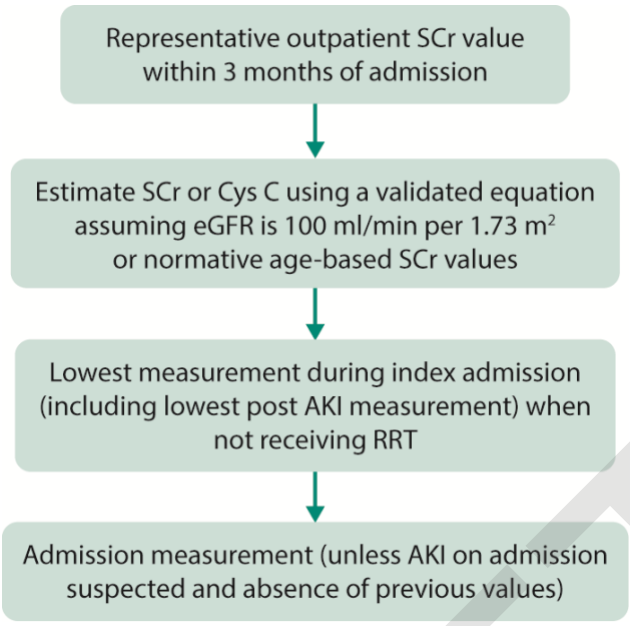
Representative outpatient SCr value within 3 months of admission
Estimate SCr or Cys C using a validated equation assuming eGFR is 100 ml/min per 1.73 m²
or normative age-based SCr values
Lowest measurement during index admission (including lowest post AKI measurement) when not receiving RRT
Admission measurement (unless AKI on admission suspected and absence of previous values)

Figure 3 | Hierarchical approach to the selection of the baseline SCr value used to characterize an AKI event in children*. *A representative outpatient SCr should ideally reflect the mean, median, or most recent value within 3 months of admission or acute event.
AKI, acute kidney injury; Cys C, cystatin C; eGFR, estimated glomerular filtration rate; RRT, renal replacement therapy; SCr, serum creatinine

Practice Point 1.6.2.2: In children, specific considerations related to age are needed when determining a baseline SCr.

1.6.3. Criteria for neonatal AKI

Practice Point 1.6.3.1: The criteria for neonatal AKI include a lack of decline in SCr within the first 7 days of birth, in addition to neonatal specific increases in SCr or cystatin C levels, or reduced urine output. (Table 12).

Table 12 | Criteria for AKI in neonates (any one or more of the following within the corresponding time period)

Neonatal AKI criteria
• No decline in SCr from birth to 7 days of life • Increase in SCr by ≥0.3 mg/dl (≥26.5 µmol/l) within 48 hours • Increase in SCr by ≥1.5 times baseline that is known or presumed to have occurred within the prior 7 days • Increase in serum cystatin C by 1.25 times baseline that is known or presumed to have occurred within the prior 7 days • Serum cystatin C >2.2 mg/dl • Urine output of less than 1.0 ml/kg/h for ≥24 hours

AKI, acute kidney injury; SCr, serum creatinine

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1.6.4. AKI staging in neonates

Practice Point 1.6.4.1: In neonates, the severity of AKI is staged according to individual components or combinations of the following SCr and urine output criteria (Table 13).

Table 13 | AKI staging criteria in neonates

Functional criteria			
Serum creatinine		**Urine output**	
Stage	**Criteria**	**Stage**	**Criteria**
C1	No decline in SCr from birth to 7 days of life, *Or* ≥0.3 mg/dl (26.5 µmol/l) increase, *Or* 1.5–1.9 times baseline	**U1**	>0.5 and ≤1.0 ml/kg/h for 24 h
C2	2–2.9 times baseline	**U2**	>0.3 and ≤0.5 ml/kg/h for 24 h
C3	≥3 times baseline *Or* Increase in SCr to ≥2.5 mg/dl (220 µmol/l), *Or* Initiation of RRT	**U3**	≤0.3 ml/kg/h for 24 h

C1-C3 indicates AKI severity stage according to serum creatinine (SCr) criteria, U1-U3 indicates AKI severity stage according to urine output criteria, B-/B+ indicates staging by absence or presence of an elevated damage biomarker. AKI, acute kidney injury; RRT, renal replacement therapy

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CHAPTER 2. AKI PREDICTION, RISK STRATIFICATION, AND DIAGNOSTIC EVALUATION

2.1. Risk prediction models

Recommendation 2.1.1: We suggest using externally validated clinical risk models to identify children and adults at increased risk of AKI and guide the use of kidney-protective strategies *(2C).*

Recommendation 2.1.2: We recommend using externally validated clinical risk models to identify adults at risk of receiving renal replacement therapy (RRT) for AKI to inform patient choices and shared decision making about their care *(1C)*.

Practice Point 2.1.1: In community and low-resource settings, simplified AKI risk scores can support early identification and management of adults at risk for community-acquired AKI.

Practice Point 2.1.2: The performance of electronic health record (EHR)-based AKI risk models should be tested in the settings they will be deployed. Harmonizing terminology and data structure within EHR systems and reassessment of performance over time is needed to ensure predictive accuracy in a local setting and over time.

2.2. Electronic AKI alerts

Recommendation 2.2.1: We recommend against delivering interruptive, creatinine-based electronic alerts for AKI in isolation without systematic strategies for response in routine clinical care of adults (*1B*).

2.3. Kidney functional testing

Practice Point 2.3.1: Assessment of kidney functional reserve before a potential exposure may help to identify children and adults with an increased likelihood of developing AKI.

Recommendation 2.3.1: We suggest using the furosemide stress test (FST) to assess the risk of progression to Stage 3 AKI, including RRT in adults (*2C*) and children (*2B*) with Stage 1 or 2 AKI who are euvolemic or hypervolemic.

Recommendation 2.3.2: We suggest calculating kinetic estimated glomerular filtration rate (KeGFR) in hospitalized adults with or at risk of AKI when an estimate of GFR under non-steady-state conditions will affect clinical decision-making *(2B)*.

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2.4. Biomarkers for AKI risk stratification

Practice Point 2.4.1: Baseline albuminuria (measured by urine albumin-to-creatinine ratio [UACR or dipstick protein testing]) offers additional prognostic value to eGFR for evaluating AKI risk in adults across various settings.

Recommendation 2.4.1: In acute care settings where children and adults are susceptible to AKI, we suggest using biomarkers of kidney tubular stress or damage according to their clinically validated and regulatory approved indication for the early identification of people at risk of moderate or severe AKI, to inform targeted kidney-protective strategies (*adults: 2B; children: 2C)*.

Practice Point 2.4.2: Biomarkers of kidney stress (e.g., urine [TIMP-2]*[IGFBP7]) can be used to assess the risk of moderate-to-severe AKI in critically ill adults, especially within the first 12 hours of ICU admission or after high-risk events including major surgery or sepsis.

Practice Point 2.4.3: Biomarkers of kidney damage (e.g., urine NGAL) can be used to identify children and adults at high risk of severe AKI in hospital settings.

2.5. Tests for AKI etiology and diagnostic evaluation

Recommendation 2.5.1. In adults with AKI, we suggest urine microscopy as part of the diagnostic evaluation, particularly when the etiology is unclear or intrinsic kidney disease is suspected, as urine sediment examination can provide diagnostic and prognostic information that complements clinical assessment and other laboratory studies *(2D)*.

Practice Point 2.5.1: Muddy brown granular casts and renal tubular epithelial cells can assist in distinguishing acute tubular injury (ATI) from hemodynamic-mediated AKI and predict progression to severe AKI.

Practice Point 2.5.2: Urine eosinophil testing has low sensitivity and moderate specificity, limiting its diagnostic value particularly for excluding a diagnosis of acute interstitial nephritis (AIN).

Practice Point 2.5.3: Urinary inflammatory cytokines may be useful in distinguishing AIN from other causes of AKI or AKD in adults.

Practice Point 2.5.4: Urine chemistries, including fractional excretion of sodium (FeNa) and fractional excretion of urea (FeUrea) should be reserved for use in differentiating hemodynamic-mediated (prerenal) AKI from ATI in selected clinical scenarios and groups of children and adults with AKI, due to their limited overall clinical utility.

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Practice Point 2.5.5: In adults with cirrhosis-associated AKI, FeNa can be an adjunctive tool to distinguish hepatorenal syndrome from ATI when interpreted in the appropriate clinical context.

Practice Point 2.5.6: In adults with cirrhosis-associated AKI, urinary or plasma NGAL may be an adjunct to help differentiate between ATI and hepatorenal syndrome, particularly when clinical features or response to volume expansion or vasoconstrictor therapy are equivocal.

Practice Point 2.5.7: Kidney biopsy should be considered for children and adults with unexplained AKI when clinical evaluation does not clearly differentiate among potential causes or the findings are expected to influence management decisions.

Practice Point 2.5.8: Kidney Doppler ultrasound, including measurement of renal resistive index (RRI), may aid in risk stratification for AKI progression and severity, particularly in critically ill populations.

Practice Point 2.5.9: In hospitalized or critically ill patients with AKI, point-of-care ultrasound (POCUS) may assist in assessing volume status and distinguishing volume responsive AKI from intrinsic AKI.

2.6. Considerations specific to children

Practice Point 2.6.1: Children at increased risk for community-acquired AKI should undergo a kidney health assessment during episodes of acute illness.

Recommendation 2.6.1: For critically ill children at risk for AKI, we suggest using the renal angina index (RAI) to identify children at high risk of severe AKI and RRT *(2B)*.

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CHAPTER 3. PREVENTION AND TREATMENT OF AKI

3.1 Fluid management

Recommendation 3.1.1: We recommend using crystalloids rather than colloids (albumin, gelatin, or starches) as initial management for intravascular volume expansion in children and adults at risk of or with AKI or AKD (*1B*).

Recommendation 3.1.2: We recommend using buffered crystalloids instead of 0.9% saline for volume expansion in the absence of traumatic brain injury in children and adults at risk of or with AKI or AKD (*1B*).

Recommendation 3.1.3: For children and adults with AKI or AKD who have severe metabolic acidosis with acidemia (pH <7.20), we suggest the use of intravenous bicarbonate over RRT unless there is another urgent indication for RRT (*2C*).

Practice Point 3.1.1: Offer oral rehydration to children and adults at risk of or with AKI or AKD being managed in settings where volume expansion with intravenous fluid administration is not possible or practical.

Recommendation 3.1.4: For adults undergoing elective major abdominal surgery, we recommend a liberal intravenous fluid management strategy, aiming for a positive fluid balance gain of 1–2 kg at 24 hours after surgery, over a restrictive strategy (net zero fluid balance) (*1B*).

3.2 Hemodynamic management

Practice Point 3.2.1: Use hemodynamic monitoring strategies for adults at risk of and with AKI to assess adequate organ perfusion and oxygen delivery, which will be context-sensitive and resource availability dependent.

Practice Point 3.2.2: Use vasoactive medications in conjunction with fluids in children and adults with hypotension not responsive to initial fluid administration and who are at risk of or have AKI.

Recommendation 3.2.1: We suggest a mean arterial pressure (MAP) of >65 mm Hg as a target to guide fluid and vasopressor administration in critically ill adults at high risk of or with AKI (*2C*).

Practice Point 3.2.3: Higher or lower MAP targets may be appropriate for individual critically ill adults, for instance to maintain renal perfusion in patients with chronic hypertension and to avoid adverse effects of excessive vasopressor therapy in patients with chronic hypotension.

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Recommendation 3.2.2: We recommend against using low-dose dopamine for kidney protection in children or adults at risk of or with AKI or AKD (*1A*).

Recommendation 3.2.3: We recommend the use of a multicomponent kidney-protection strategy in adult surgical patients at high risk for AKI identified by clinical factors and biomarkers (Figure 9; *1B*).

Practice Point 3.2.4: In children and adults with established AKI or AKD, kidney-protection strategies should be considered.

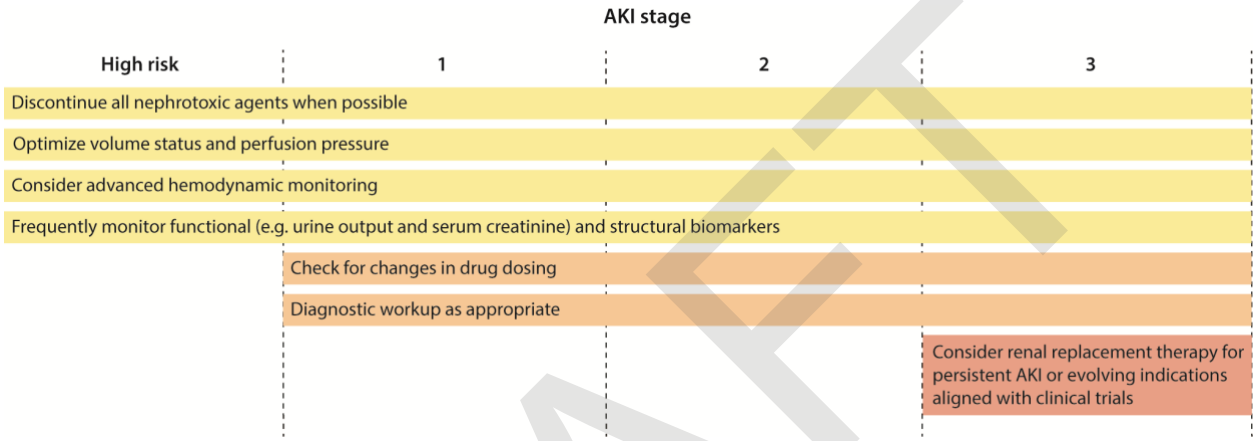
AKI stage
High risk
1
2
3
Discontinue all nephrotoxic agents when possible
Optimize volume status and perfusion pressure
Consider advanced hemodynamic monitoring
Frequently monitor functional (e.g. urine output and serum creatinine) and structural biomarkers
Check for changes in drug dosing
Diagnostic workup as appropriate
Consider renal replacement therapy for persistent AKI or evolving indications aligned with clinical trials

Figure 9 | Multicomponent kidney protection strategy for prevention and management of AKI. AKI, acute kidney injury

3.3 Use of diuretics

Recommendation 3.3.1: We suggest use of diuretics in the management of clinically significant volume overload of children and adults with or at risk of AKI or AKD (*2B*).

Practice Point 3.3.1: Intermittent boluses, rather than continuous infusions of loop diuretics, are appropriate as the initial diuretic management strategy in adults with or at risk of AKI or AKD.

Recommendation 3.3.2: We recommend initial use of diuretics in preference to extracorporeal fluid removal for adults at risk of or with AKI or AKD who have clinically significant volume overload in the absence of another indication for RRT (*1C*).

3.4 Glucose control

Practice Point 3.4.1: Insulin therapy targeting a plasma glucose level of 140–180 mg/dl (7.8–10 mmol/) is acceptable over more aggressive targets in critically ill children and adults with or at risk of AKI or AKD.

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3.5 Prevention of cardiac surgery-associated AKI

Recommendation 3.5.1: In adults without advanced CKD having cardiac surgery, we suggest that prophylactic intravenous amino acid administration can be used to prevent AKI (*2A*).

Recommendation 3.5.2: We suggest remote ischemic preconditioning for patients at high risk for AKI undergoing cardiac surgery without propofol anesthesia to prevent AKI in children (*2D*) and adults (*2B*).

3.6 Hepatorenal syndrome-associated AKI

Recommendation 3.6.1: We recommend the use of vasoconstrictor therapy for adults with hepatorenal syndrome-associated AKI (*1C*).

Practice Point 3.6.1: The choice of vasoconstrictor should be based on the clinical care context and patient condition. Terlipressin or norepinephrine are preferrable therapies; midodrine with octreotide can be used as an alternative for adults if terlipressin and norepinephrine are unavailable.

3.7 Tumor lysis syndrome-associated AKI

Practice Point 3.7.1: Volume expansion without urinary alkalinization using intravenous crystalloids should be done in children and adults with or at risk of tumor lysis syndrome.

Recommendation 3.7.1: In children and adults with or at high risk of tumor lysis syndrome, we recommend rasburicase over allopurinol or febuxostat, if not contraindicated due to glucose 6-phosphate dehydrogenase (G6PD) deficiency (*1B*).

Practice Point 3.7.2: In children and adults at lower risk of tumor lysis syndrome, or when rasburicase is contraindicated or inaccessible, xanthine oxidase inhibitors may be used.

3.8 Rhabdomyolysis- and hemolysis-associated AKI

Practice Point 3.8.1: Use intravenous crystalloids for volume expansion in children and adults at risk of or with heme pigment nephropathy due to rhabdomyolysis or hemolysis.

3.9 Nutritional intervention in AKI

Practice Point 3.9.1: Nutrition should be provided preferentially via the enteral route in children and adults at risk of or with AKI or AKD.

Practice Point 3.9.2: Avoid restriction of protein intake with the aim of preventing or delaying initiation of RRT in children and adults with AKI or AKD.

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Practice Point 3.9.3: Excessive protein intake should be avoided in adults with AKI or AKD.

Practice Point 3.9.4: Caloric targets do not need to be changed due to AKI or AKD in children or adults, unless they are receiving RRT.

Practice Point 3.9.5: Regular review and supplementation of water-soluble vitamins and micronutrients should be considered in children and adults receiving continuous RRT (CRRT).

3.10 AKI in pregnancy

Practice Point 3.10.1: Pregnant women with AKI or AKD require specific treatments, including consideration of early delivery.

3.11 Environmental and tropical AKI

Practice Point 3.11.1: For children and adults presenting with AKD or AKI in tropical and subtropical regions, evaluate for region-specific infectious and environmental causes and initiate early disease-specific therapy in addition to standard supportive management of AKI.

Practice Point 3.11.2: For children and adults presenting with AKD or AKI in regions where traditional medicines and toxic chemicals are used, include AKI due to toxins in the differential diagnosis.

Practice Point 3.11.3: For children and adults presenting with AKD or AKI following prolonged exposure to high temperatures, consider heat injury as a cause of AKI.

3.12 Considerations specific in children

3.12.1 Hemodynamic management

Practice Point 3.12.1.1: Use age-appropriate blood pressure targets to guide hemodynamic management in children at risk or with AKI.

3.12.2 Nutritional intervention in AKI

Practice Point 3.12.2.1.: In children with AKI or AKD, age-recommended protein targets can be used without protein restriction, and a minimum daily protein intake of 2.5 grams/kg should be maintained for children receiving CRRT.

Practice Point 3.12.2.2: Supplement water-soluble vitamins routinely in children receiving CRRT.

3.12.3 Hepatorenal syndrome-associated AKI

Practice Point 3.12.3.1: It is reasonable to use terlipressin or norepinephrine for children with hepatorenal syndrome-associated AKI depending on the clinical care context and patient condition.

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3.12.4 Theophylline use in neonates

Recommendation 3.12.4.1: We recommend a single dose of theophylline be given to neonates with severe perinatal asphyxia for the prevention of AKI (*1A*).

3.12.5 Use of nitric oxide in children

Recommendation 3.12.5.1: We recommend against routine use of inhaled nitric oxide to prevent cardiac surgery-associated AKI in children with low-complexity cardiac lesions and no signs of pulmonary hypertension or right ventricular dysfunction undergoing cardiopulmonary bypass (*1C*).

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CHAPTER 4. DRUG- AND NEPHROTOXIN-ASSOCIATED AKI

4.1. Categorization and classification of medications associated with AKI

Practice Point 4.1.1: Drugs that may contribute to AKI can be classified into one of 4 categories based on kidney function and damage biomarkers assessed at the time of exposure (Figure 11).

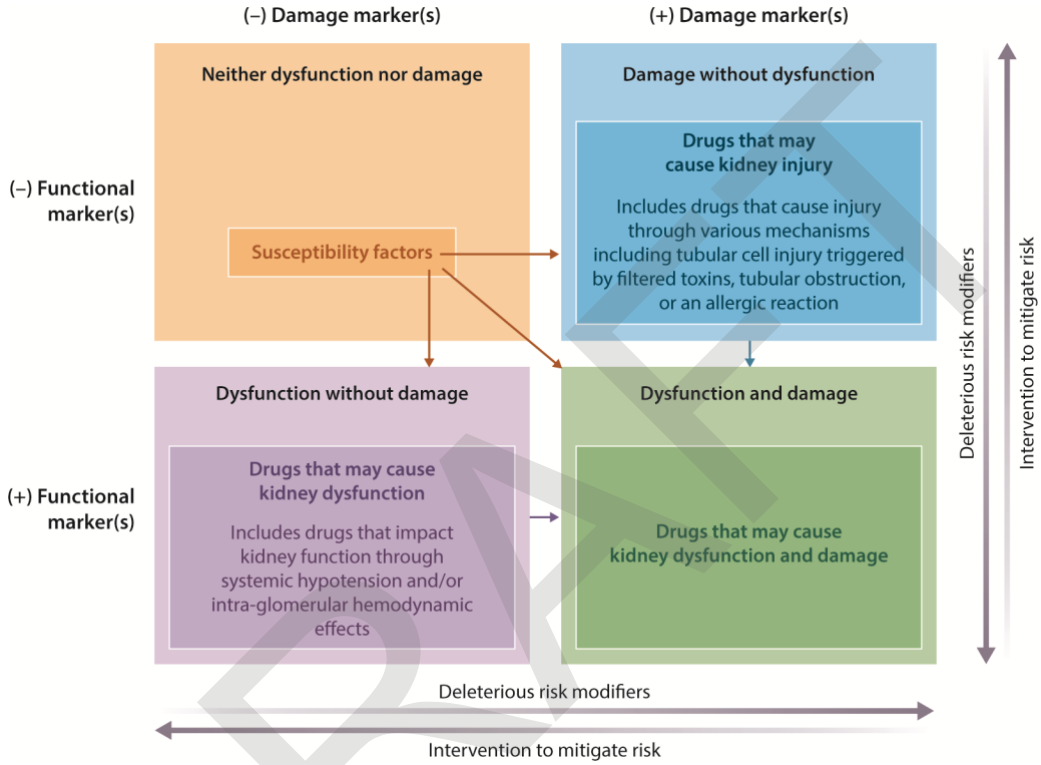
(–) Damage marker(s)
(+) Damage marker(s)
Neither dysfunction nor damage
Damage without dysfunction
(–) Functional marker(s)
Drugs that may cause kidney injury
Includes drugs that cause injury through various mechanisms including tubular cell injury triggered by filtered toxins, tubular obstruction, or an allergic reaction
Susceptibility factors
Dysfunction without damage
Dysfunction and damage
(+) Functional marker(s)
Drugs that may cause kidney dysfunction
Includes drugs that impact kidney function through systemic hypotension and/or intra-glomerular hemodynamic effects
Drugs that may cause kidney dysfunction and damage
Deleterious risk modifiers
Intervention to mitigate risk
Deleterious risk modifiers
Intervention to mitigate risk

Figure 11 | Classifying drugs that potentially cause AKI.[530] Iterative classification of agents that have potential to cause kidney dysfunction/abnormal kidney function or kidney injury or both. Functional and injury biomarkers have a role in distinguishing among the different pathophysiological processes. Examples of deleterious risk modifiers are duration of therapy, drug burden, hypotension, and pharmaco/pharmacodynamic interactions. Examples of interventions to mitigate risk are daily dynamic prescribing, kidney monitoring, and patient and provider education. Susceptibility factors include those listed in Table 14 in Chapter 2. Any final impact depends on underlying susceptibility, associated risk factors, clinical context, drug management, and modifying factors. Examples of drugs that correspond to the relevant categories above include trimethoprim, cimetidine (neither dysfunction nor damage); angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers (dysfunction without damage); aminoglycoside, acyclovir, vascular endothelial growth factor antagonists (damage without dysfunction); and nonsteroidal anti-inflammatory drugs (dysfunction and damage). AKI, acute kidney injury. Adapted from Ostermann et al. 2020.[531]

4.2. Kidney protective strategies

Recommendation 4.2.1: For children or adults with or at risk of AKI, we recommend drug and nephrotoxin stewardship using a multimodal approach (*1C*).

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Practice Point 4.2.1: Strategies to manage drug-related acute kidney disease include:

a) **discontinuation of offending nephrotoxic agents known to cause kidney damage, if possible;**
b) **provision of a therapeutic equivalent alternative that is less nephrotoxic, if available and necessary;**
c) **reduction in dose if drug continuation is necessary for those drugs with a dose dependent direct nephrotoxic effect.**

Practice Point 4.2.2: Therapeutic drug monitoring is a component of multimodal stewardship that involves serial assessments of drug concentrations in children and adults receiving potentially nephrotoxic drugs, drugs excreted by the kidneys, and drugs with narrow therapeutic margins or low therapeutic indices.

Practice Point 4.2.3: Surveillance for pharmacokinetic and pharmacodynamic drug-drug interactions that increase the risk of AKI is a component of multimodal stewardship.

Practice Point 4.2.4: Intravenous hydration strategies may be used for the prevention of drug-induced crystalline nephropathies as part of multimodal stewardship.

4.3. Implementation of kidney protective strategies

Practice Point 4.3.1: Pharmacists should perform medication reconciliation and medication regimen reviews and perform drug and nephrotoxin stewardship for hospitalized children and adults with or at risk of AKI.

Practice Point 4.3.2: Clinical decision support systems (CDSS) can be an effective tool to facilitate drug and nephrotoxin stewardship strategies in children and adults to prevent drug-associated AKI or the development of adverse reactions from drugs excreted by the kidney.

4.4 Biomarker characterization of drug-related AKI

Practice Point 4.4.1: Biomarkers of tubular damage are approved for monitoring of drug-induced AKI.

Practice Point 4.4.2: Biomarkers may be useful for differentiating mechanisms and etiologies of drug-related kidney diseases in children and adults.

4.5. Management of drugs eliminated by the kidneys

Practice Point 4.5.1: Dosing of drugs excreted by the kidneys should not be based on creatinine clearance or glomerular filtration rate (GFR) estimated using equations that assume a steady state of creatinine production and clearance in children and adults children with developing or resolving AKI or AKD.

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Practice Point 4.5.2: Trends in SCr and urine output should be used to guide dosing of drugs excreted by the kidney. In adults with AKI, calculation of a KeGFR may be useful when sufficient SCr measurements are available.

The Work Group agrees with the following practice point related to drug dosing from the *KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of CKD* and believes it also applies to people with AKI and AKD.

Practice Point 4.5.3: Consider and adapt drug dosing in people where GFR, non-GFR determinants of the filtration markers, or volume of distribution are not in a steady state.

Practice Point 4.5.4: Assess and adjust drug dosing in children and adults receiving CRRT based on drug-, patient-, and RRT-related factors (Table 34).

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Table 34 | Drug-, patient-, and RRT-related factors to consider when determining drug doses for people receiving CRRT

Drug-related factors	• Medications eliminated by the kidney with volume of distribution <0.7 l/kg and/or protein-binding <80% are likely to be removed with CRRT and may require supplemental dosing with CRRT use. • Molecular weight of a drug is an important consideration when using CRRT diffusive techniques compared to convective techniques because the diffusion coefficient, or saturation coefficient (Sd or SA) is inversely proportional to the molecular weight such that, as the SA decreases, the molecular weight increases. Conversely, convective transport across modern membranes is independent of molecular weight in convective hemofiltration techniques.[594, 595] • Most drugs have a molecular weight <2000 Daltons and are removed to some extent with newer high-flux and super high-flux dialyzers that have a pore size between 10,000–30,000 (likely diffusion technique, as well) • Administering supplement doses for drugs with >30%–40% post-hemodialysis removal is suggested. • Optimal dosage regimens for medications eliminated by the kidney and nephrotoxic medications (e.g., digoxin, vancomycin, aminoglycosides, and calcineurin inhibitors) can be achieved by performing therapeutic drug monitoring in people who are critically ill receiving RRT. • For antibiotic dose adjustments during AKI and RRT, be mindful of pharmacokinetic target concentration attainment and optimizing pharmacodynamic effects with consideration to the antibiotic concentration and time dependent bactericidal effects.
Patient-related factors	• Hypoalbuminemia affects drugs that are highly bound to albumin, by increasing free fraction of the drug leading to increased clearance and volume of distribution. • Fluid resuscitation, and capillary leak increase the volume of distribution of hydrophilic drugs, for example in people with sepsis. This may require a loading dose in the range of 25% more than usual. • People with significant urine output (e.g., >20 ml/hr or 500 ml/day), should have clearance from the residual urine volume added to RRT clearance calculations to determine total drug clearance for the person. • Non-kidney drug clearance can be affected by RRT for AKI. Drugs eliminated by the liver and formed metabolites may accumulate during AKI, while RRT can possibly increase CYP3A4 activity. Estimating non-kidney clearance in people who are critically ill is challenging without assessing serum drug levels due to the various pathways involved in drug metabolism and clearance.

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*RRT-related factors**	• Effluent flow rate determines drug clearance in CRRT given it is slower than the blood flow rate and more drug removal occurs with faster effluent flow rates.[596] • If RRT is <25% of the patient's clearance (sum of residual kidney and non-kidney), then RRT appears not to add significantly to person's drug elimination process.[595] • RRT modality affects drug clearance such that when a similar blood flow rate is used, drug elimination by RRT can be ordered from the highest to lowest as follows: CVVHDF > CVVH > IHD.[594] • For CRRT, clearance can be estimated by checking the run time and subtracting the down time. • Replacement fluid is commonly provided in convective techniques of RRT, either pre- or post-dilution modes. Pre-dilution mode reduces drug clearance more than post-dilution by approximately 15%.[594] • Hemofilter lifespan can affect solute clearance (i.e., older filters provide less clearance). • Membrane types affect adsorption and adsorption is inversely correlated to effluent flow rate.[594, 597, 598] • Drug removal estimates for IHD are not equivalent to CRRT. When suing drug removal estimates from primary or secondary sources, it is important to confirm that the RRT modality, technique, and settings are the same as the patient scenario being evaluated.

*RRT related factors do not apply to children due to the size of the extracorporeal volume. AKI, acute kidney injury; CRRT, continuous renal replacement therapy; CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration, IHD, intermittent hemodialysis, PIRRT, prolonged intermittent renal replacement therapy; RRT, renal replacement therapy

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4.6. AKI following other nephrotoxic exposures

Practice Point 4.6.1: In children and adults presenting with community-acquired AKI, perform a thorough social, occupational, and demographic history to understand potential exposures to pesticides and environmental exposures as a possible cause of AKI.

Practice Point 4.6.2: Determine and limit the use of natural products that have the potential to contribute to AKI and AKD through patient-centered discussions.

4.7. Contrast-associated AKI (CA-AKI): Recognition

Practice Point 4.7.1: Consider the differential diagnosis of post-contrast AKI, which may have causes other than contrast exposure.

4.8. Contrast-associated AKI: Risk assessment

Practice Point 4.8.1: Use validated tools to assess the risk of AKI in adults receiving intra-arterial radiocontrast for cardiac procedures.

Practice Point 4.8.2: Assess children and adults being considered for intravenous radiocontrast administration for risk factors for contrast-associated AKI, and in particular screen for preexisting impairment of kidney function.

4.9. Contrast-associated AKI: Prevention

4.9.1. Choice of imaging technique

Practice Point 4.9.1.1: Following a risk assessment, the decision to administer intravascular contrast for a diagnostic or interventional procedure should be made weighing the risks versus benefits of the procedure. Where the perceived benefit exceeds the risk, contrast procedures should not be deferred or delayed. However, alternative imaging methods should be used for people with or at high risk of contrast-associated AKI (CA-AKI) (Figure 12).

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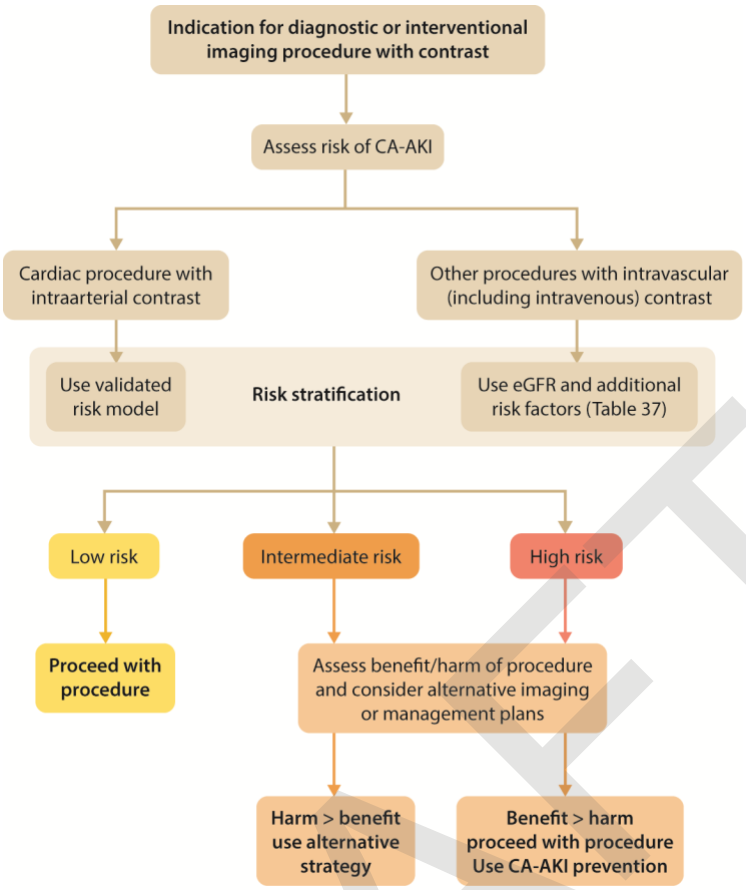
Indication for diagnostic or interventional imaging procedure with contrast
Assess risk of CA-AKI
Cardiac procedure with intraarterial contrast
Other procedures with intravascular (including intravenous) contrast
Use validated risk model
Risk stratification
Use eGFR and additional risk factors (Table 37)
Low risk
Intermediate risk
High risk
Proceed with procedure
Assess benefit/harm of procedure and consider alternative imaging or management plans
Harm > benefit use alternative strategy
Benefit > harm proceed with procedure Use CA-AKI prevention

Figure 12 | Approach to risk assessment for CA-AKI with diagnostic or interventional contrast imaging procedures. CA-AKI, contrast-associated acute kidney injury

Practice Point 4.9.1.2: Iso-osmolar or low-osmolar iodinated contrast media may be used in children and adults at risk of CA-AKI (*1B*).

Practice Point 4.9.1.3: For children and adults at high risk of CA-AKI, use the lowest possible dose of intravascular radiocontrast to achieve adequate imaging.

4.9.2. Contrast-associated AKI Prevention: Fluid administration

Practice Point 4.9.2.1: For children and adults at high risk of CA-AKI, incorporate volume status assessment into intravenous hydration management strategies to reduce the risk of AKI.

Recommendation 4.9.2.1: For adults at high risk of AKI without fluid overload undergoing intravascular iodinated contrast-based procedures, we recommend prophylactic periprocedural volume expansion with 0.9% saline over hypotonic solutions (e.g., 0.45% saline), sodium bicarbonate, or no intravenous hydration *(1B)*.

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Practice Point 4.9.2.2: In the absence of volume overload, it is appropriate to hold diuretics when administering isotonic crystalloid to prevent CA-AKI in adults at high risk.

4.9.3 Prophylactic therapies: Medication management

The Work Group agrees with the following practice point and radiology guideline statements related to the intravenous administration of radiocontrast from the *KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of CKD*.

Practice Point 4.9.3.1: The intravenous administration of radiocontrast media can be managed in accordance with consensus statements from the radiology societies in people with AKI or GFR <60 ml/min per 1.73 m^2 (CKD G3a–G5) undergoing elective investigation.

The Work Group refers the reader to the most recent radiology guidelines specifically noting the difference between intravenous and intra-arterial radiocontrast:

- Use of low-osmolality contrast media and iso-osmolarity contrast media
- Use of minimum radiocontrast dose to achieve a diagnostic study
- Withdrawal of nonessential potentially nephrotoxic medications (e.g., NSAIDs, diuretics, aminoglycosides, amphotericin, platins, zoledronate, and methotrexate) in people with AKI or eGFR <30 ml/min per 1.73 m^2 for 24–48 hours before and 48 hours after radiocontrast exposure
- In people with eGFR >30 ml/min per 1.73 m^2 and without evidence of AKI, metformin need not be stopped before iodinated contrast media (ICM) administration, and there is no need for testing to evaluate GFR afterward. For people with AKI or an eGFR ≤30 ml/min per 1.73 m^2, it remains appropriate to stop metformin at the time of or before ICM injection and should not be restarted for at least 48 hours and only then if GFR remains stable and the ongoing use of metformin has been reassessed by the clinical team.[673]
- Consideration of avoiding dehydration for people not undergoing dialysis and who have eGFR <30 ml/min per 1.73 m^2 or AKI and receiving intravenous contrast.[674, 675]
- Use of N-acetylcysteine, ascorbic acid, furosemide, dopamine, fenoldopam, or calcium channel blockers as preventative measures of CA-AKI has not been shown to be a consistent benefit.[613]
- Prophylactic pericontrast hemodialysis has been shown to be potentially harmful and is not recommended.[613]

Recommendation 4.9.3.1: We suggest not routinely withholding renin-angiotensin system inhibitors (RASi) before procedures with iodinated radiocontrast administration in adults (*2C*).

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4.10 Temporary withdrawal of medications to prevent AKI during major surgery

Recommendation 4.10.1: We suggest not routinely withholding renin-angiotensin system inhibitors (RASi) to prevent AKI in adults having elective major cardiac *(2D)* or non-cardiac surgery *(2B)*.

4.11 Medication management during intercurrent illness or "sick day protocols"

Recommendation 4.11.1: We suggest temporarily stopping specific classes of drugs in the context of acute illnesses that predispose to volume depletion, to prevent AKI caused by hypovolemia (*2D*).

The Work Group also agrees with the following practice point from Section 4.3 of the *KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of CKD* and believe it also applies to people with AKI or AKD:[16]

Practice Point 4.11.1: If medications are discontinued during an acute illness, communicate a clear plan of when to restart the discontinued medications to the affected person and healthcare professionals, and ensure documentation in the medical record.

4.12. Considerations specific to children

4.12.1 Biomarker characterization of drug-related AKI

Practice Point 4.12.1.1: Urine biomarkers of kidney damage can be helpful in detecting nephrotoxin-associated AKI in newborns..

4.12.2. Management of drugs eliminated by the kidney

Practice Point 4.12.2.1: Trends in SCr and urine output can be used to guide dosing of drugs excreted by the kidney. The validity of KeGFR equations to inform drug dosing in children is uncertain.

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CHAPTER 5. RENAL REPLACEMENT THERAPY

5.1. Starting renal replacement therapy (RRT)

Practice Point 5.1.1: For children and adults with AKI, a process of informed shared decision-making should be used with patients, family, caregivers, and healthcare professionals on the relative merit and risk of treatment with RRT.

Recommendation 5.1.1: For adults with AKI, we recommend a strategy of deferred timing of RRT initiation as preferred over a strategy of early (pre-emptive) RRT initiation (*1C*).

Practice Point 5.1.2: For children and adults with AKI and high probability of requiring RRT, planning for RRT should be considered before indications are met, including, where applicable and available, transfer to centers with nephrology and RRT services.

Practice Point 5.1.3: For children and adults with AKI and medically refractory fluid, electrolyte, acid-base, and/or metabolic complications (e.g., uremia), initiate RRT if consistent with patient preferences and goals of care.

Practice Point 5.1.4: Among patients with hepatic encephalopathy (grade ≥2) due to acute or acute-on-chronic liver failure, initiation of continuous RRT (CRRT) to manage hyperammonemia may be considered even when conventional RRT indications are absent.

Practice Point 5.1.5: For critically ill children and adults with AKI, a time-limited trial of RRT can be started if uremic and/or metabolic complications are plausibly confounding neurological evaluation or chances of awakening from coma.

Practice Point 5.1.6: For children and adults with AKI, particularly those receiving vasoactive support, identify and treat modifiable factors and mitigators of hemodynamic instability at the commencement of RRT.

5.2. RRT modality

Practice Point 5.2.1: The initial selection of RRT modality in children and adults with AKI, including CRRT, intermittent RRT (IRRT), or acute peritoneal dialysis (PD), should integrate patient characteristics, clinical context, local expertise, and resource availability.

Recommendation 5.2.1: For critically ill adults with AKI and hemodynamic instability, we suggest using CRRT or acute PD over conventional IRRT *(2C)*.

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Practice Point: 5.2.2: CRRT is preferable to conventional IRRT for critically ill children and adults with AKI and acute brain injury or other causes or risks of increased intracranial pressure (ICP) or cerebral edema.

Practice Point 5.2.3: For children and adults with AKI, particularly those requiring vasoactive support, identify and treat modifiable factors and mitigators of hemodynamic instability during RRT.

Practice Point 5.2.4: Prolonged IRRT (PIRRT) is an acceptable alternative to CRRT as the initial RRT modality for hemodynamically unstable, critically ill adults with AKI.

Practice Point 5.2.5: Transition from CRRT to IRRT can be considered when children and adults who have not recovered from AKI are physiologically and metabolically able to tolerate IRRT and the risks of intracranial hypertension or cerebral edema, if applicable, are resolved.

5.3. RRT dose-intensity

Recommendation 5.3.1: We recommend delivering an effluent volume of 20-25 ml/kg/h over higher volumes for solute clearance in adults receiving CRRT, or a Kt/V of 3.9 per week over higher urea clearance in adults receiving IRRT or PIRRT for AKI (*1B*).

Practice Point 5.3.1: An initial CRRT dose-intensity for adults with high body mass index (BMI; e.g., ≥30 kg/m^2) based on ideal or adjusted body weight, rather than actual body weight, can be used to avoid delivery of excess CRRT dose-intensity.

Recommendation 5.3.2: We recommend not prescribing high-volume hemofiltration (HVHF) compared with standard CRRT dose-intensity for critically ill adults with AKI in the setting of sepsis or septic shock (*1B*).

Practice Point 5.3.2: The adequacy of the RRT dose-intensity to correct for electrolyte, acid-base, and metabolic (e.g., nitrogenous waste) derangements should be reviewed daily for CRRT and prior to starting each RRT session for IRRT and the prescription adjusted when needed.

Practice Point 5.3.3: When using acute PD for adults with AKI, deliver a weekly Kt/V of 2.2 (18-24 l PD fluid/day) over higher doses.

Practice Point 5.3.4: In adults with AKI, the initial PD prescription, including duration of cycle time and glucose concentration of PD fluid, may need to be modified to rapidly correct acid-base, electrolyte, metabolic, or fluid complications in adults with AKI.

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5.4 Catheters for RRT

Practice Point 5.4.1: Vascular access for RRT, including type, size, length, and site of catheter placement, should consider feasibility and weigh the risks of catheter colonization/infection or bleeding with the desire to maintain catheter/circuit patency in children and adults.

Practice Point 5.4.2: Adoption of standardized care bundles for dialysis catheter insertion and maintenance can reduce the risk of complications.

Practice Point 5.4.3: Use of existing arteriovenous fistulas/grafts may be suitable for IRRT in children and adults to avoid new dialysis catheter placement.

Practice Point 5.4.4: It is preferable to avoid using existing arteriovenous (AV) fistulas/grafts for CRRT in children or adults, due to concern for needle dislodgement or arteriovenous fistulae/graft damage with prolonged cannulation.

Practice Point 5.4.5: The decision on how to replace poorly performing uncuffed nontunneled dialysis catheters should be individualized. The options include a new venipuncture or, in select cases, a guidewire exchange of the existing dialysis catheter.

Practice Point 5.4.6: Do not perform routine or scheduled change of dialysis catheters to reduce the risk of catheter-related infection.

Practice Point 5.4.7: In circumstances where prolonged indications for RRT are anticipated, a cuffed tunneled catheter can be considered when initiating RRT for AKI, particularly for children.

Practice Point 5.4.8: For patients who remain dialysis dependent with low probability of resolution of AKI or patients being prepared for hospital discharge, transition to a cuffed tunneled catheter should be undertaken.

5.5. Anticoagulation for RRT

Recommendation 5.5.1: Where available, we recommend using regional citrate anticoagulation rather than heparin in children and adults receiving CRRT who do not have contraindications to citrate *(1B)*.

Practice Point 5.5.1: Unfractionated heparin, epoprostenol, or nafamostat mesylate are acceptable alternatives to regional citrate anticoagulation for children and adults receiving CRRT if citrate is contraindicated or not available.

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Practice Point 5.5.2: The addition of regional citrate anticoagulation to systematic anticoagulation can be appropriate for children and adults with hypercoagulable states receiving CRRT.

Practice Point 5.5.3: Unfractionated or low-molecular-weight heparin should be considered for children and adults receiving intermittent hemodialysis (IHD) or PIRRT without increased bleeding when not already receiving systematic anticoagulation.

Practice Point 5.5.4: Anticoagulation with argatroban, danaparoid, or bivalirudin, rather than other non-heparin anticoagulants, should be used in adults receiving RRT with acute heparin-induced thrombocytopenia (HIT) who require systemic anticoagulation.

Practice Point 5.5.5 Regional citrate anticoagulation rather than heparin or non-heparin anticoagulants is preferable in adults receiving RRT with subacute (HIT-A, HIT-B) or remote HIT, who are not receiving systemic anticoagulation and require anticoagulation to prevent clotting of the dialysis circuit.

5.6 Hemofilters for RRT

Practice Point 5.6.1: Biocompatible membrane hemofilters and dialyzers should be used in children and adults with AKI undergoing CRRT or IHD.

Practice Point 5.6.2: Non-pharmacologic strategies that may be used to maintain and maximize circuit/hemofilter lifespan include optimizing catheter position in the right atrium, use of predilution hemofiltration, and continuous venovenous hemodialysis (CVVHD) or hemodiafiltration (CVVHDF) rather than continuous venovenous hemofiltration (CVVH).

Practice Point 5.6.3: Where regional citrate or systemic heparin anticoagulation are contraindicated or not available, priming of the CRRT circuit/filter with a solution containing unfractionated heparin (UFH) may be used to increase circuit/hemofilter lifespan.

5.7. Replacement and dialysate solutions for RRT

Practice Point 5.7.1: Use bicarbonate, rather than lactate, as a buffer in dialysate and replacement fluid for CRRT in adults with AKI in the following scenarios: circulatory shock, liver failure or lactic acidemia.

Practice Point 5.7.2: CRRT dialysate and replacement solutions should be sterile. Dialysate and replacement solutions for IRRT should comply with American Association of Medical Instrumentation (AAMI) standards regarding contamination with bacteria and endotoxins.

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Practice Point 5.7.3: Locally compounded dialysate and replacement CRRT solutions should be prepared using standard quality control processes or commercially available dialysate and replacement CRRT solutions should be used to allow flexibility in achieving various goals of plasma electrolyte compositions to address most clinical circumstances.

Practice Point 5.7.4: Base the choice of dialysate and replacement CRRT solutions with specific compositions upon the goals for serum electrolyte and acid–base parameters. The use of dialysate and replacement solutions should be individualized and reassessed at frequent intervals depending upon the clinical condition of the patient to ensure that they are appropriate.

5.8. Ultrafiltration in RRT

Practice Point 5.8.1: The target ultrafiltration should be prescribed daily for CRRT and prior to each IRRT session and be frequently monitored.

Practice Point 5.8.2: The prescribed intensity of ultrafiltration (e.g., timing and rate of removal) should be individualized and consider patient characteristics, clinical context, and phase of illness.

5.9 Discontinuation of RRT

Practice Point 5.9.1: Discontinue RRT when it is no longer needed either because of evidence of resolution of AKI to the point that kidney function is adequate to meet the patient's metabolic and fluid balance demands or because RRT is no longer consistent with the patient's preferences for care.

Practice Point 5.9.2: Clinical and metabolic parameters, interdialytic SCr changes, urine output, fluid balance, other parameters of resolution of AKI, and residual kidney function can be used to guide decision-making for RRT discontinuation.

Practice Point 5.9.3: Urine output >450 ml/24 hours without exposure to diuretics or >2300 ml/24 hours with exposure to diuretics and 2-hour timed creatinine clearance ≥23 ml/min can be used to predict successful RRT discontinuation in adults.

Practice Point 5.9.4: Use of diuretic therapy prior to and following RRT discontinuation can be used to augment urine output and manage fluid balance but has not been proven to facilitate resolution of AKI.

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5.10 Quality assurance for RRT

Practice Point 5.10.1: RRT programs should include the following quality standards to reduce unnecessary variation, facilitate adoption of evidence-based practices, and support opportunities for continuous quality improvement:

- **Dedicated leadership, ideally with a medical (physician) and nursing dyad partnership.**
- **Certified training and continuous education of all healthcare professionals prescribing and delivering acute RRT.**
- **Standardized order sets for the acute prescription of RRT, including decision-support for dose-intensity of solute clearance, ultrafiltration for fluid removal, and anticoagulation strategy.**
- **Standardized charting for RRT for both conventional and electronic health records, inclusive of parameters of patient and machine solute clearance and fluid balance.**
- **Monitoring and reporting of quality and key performance measures of RRT**

Practice Point 5.10.2: Key quality performance measures of RRT include measures of effective treatment time (i.e., downtime), filter lifespan, prescribed-to-delivered dose-intensity, and ultrafiltration.

5.11 RRT with extracorporeal life support (ECLS)

Practice Point 5.11.1: Strategies for integration of RRT into existing circuits in patients receiving extracorporeal life support (ECLS) depend on clinical context, local expertise, and available technology and resources.

Practice Point 5.11.2: Most patients receiving ECLS have concomitant hemodynamic instability. For these patients, initial support with CRRT rather than IRRT may be preferential.

Practice Point 5.11.3: Fluid accumulation that is refractory to medical therapy independent of kidney function may be a reasonable indication for RRT in patients receiving ECLS.

5.12. Considerations specific for children

5.12.1 Starting renal replacement therapy (RRT)

Practice Point 5.12.1.1: In critically ill children with severe AKI, RRT initiation within 2 days of intensive care unit (ICU) admission or AKI onset should be considered as it may be associated with improved outcome.

Practice Point 5.12.1.2: In critically ill children, isolated fluid overload can be an indication for RRT initiation.

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5.12.2. RRT modality

Practice Point 5.12.2.1: Acute PD is an acceptable RRT modality and may be preferable to CRRT for children in select circumstances.

5.12.3. RRT dose-intensity

Practice Point 5.12.3.1: An initial CRRT effluent volume for children can be 25–30 ml/kg/h. Thereafter, dose-intensity can be adjusted based on the adequacy of correction of electrolyte, acid-base, and metabolic derangements.

Practice Point 5.12.3.2: The dose-intensity prescription in children receiving CRRT should be weight-based (ml/kg/h), according to either body weight at hospital or ICU admission or ideal body weight and not prescribed based on body surface area.

Practice Point 5.12.3.3: In children with AKI, PD can be initiated with a fill volume of 10–20 ml/kg and short cycle times (60–90 minutes), with gradual increases in volume and dwell time as tolerated, with continuous therapy over 24 hours for the first 1–3 days to achieve solute clearance and fluid balance goals.

Practice Point 5.12.3.4: Augmentation of initial RRT dose-intensity for CRRT is warranted when treating children with hyperammonemia. CRRT dose-intensity up to 200 ml/kg/h may be acceptable to achieve adequate clearance of ammonia. Children should be appropriately monitored for unintended solute losses during periods of augmented CRRT dose-intensity.

5.12.4. Catheters for RRT

Practice Point 5.12.4.1: In small children, including neonates with small vessel size, use of a pliable cuffed catheter, as compared to a rigid temporary catheter, may be less thrombogenic and preferred, even when the expected dialysis duration is uncertain. The cuff can be left outside the body when the projected duration of use is short.

5.12.5. Anticoagulation for RRT

Practice Point 5.12.5.1: In children requiring small catheters and circuit volume and lower blood flow rates, anticoagulation is often necessary and preferred over no anticoagulation during CRRT.

5.12.6. Hemofilters for RRT

Practice Point 5.12.6.1: Appropriately sized membranes proportional to body surface area are preferred for children with AKI receiving CRRT or IRRT.

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5.12.7. Ultrafiltration in RRT

Practice Point 5.12.7.1: In children, net ultrafiltration (UF_{NET}) should not exceed 2.5 ml/kg/h. Frequent assessment of fluid balance (i.e., every 4-6 hours) should be undertaken to evaluate tolerance for fluid removal and adjust fluid balance goals, as necessary.

5.12.8. Discontinuation of RRT

Practice Point 5.12.8.1: Urine output exceeding >0.5 ml/kg/h over 6 hours can indicate resolution of AKI and be used to predict successful RRT discontinuation in children.

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CHAPTER 6. FOLLOW-UP CARE AFTER AKI OR AKD

6.1 Planning follow-up care with people after AKI and/or AKD

Recommendation 6.1.1: We recommend coordinated follow-up for children and adults after AKI and/or AKD, with personalized care according to individual clinical context and vulnerability risks (*1B*).

Practice Point 6.1.1: Transition of care from hospital to home requires clear communication between inpatient and outpatient care teams, an identified healthcare professional for AKI follow-up, and resources for patient engagement and education about their kidney health and kidney health protection.

Practice Point 6.1.2: Provide discharge summaries for children and adults with AKI that include details of the AKI episode, status of the resolution of AKI, medication management, and follow-up plans with recommendations.

Practice Point 6.1.3: A comprehensive clinical assessment of children and adults following an episode of illness affected by AKI/AKD includes assessment of blood pressure (BP) and volume status, medication reconciliation/review, and kidney function and albuminuria after hospital discharge.

Practice Point 6.1.4: Provide children and adults (and their caregivers) with a history of AKI and/or AKD access to education about kidney health, sick day guidance and kidney care, and psychosocial support to enhance functional status and quality of life.

Recommendation 6.1.2: We suggest risk stratification of AKI survivors at hospital discharge using a validated tool to identify children and adults at high risk of CKD who may benefit from nephrology care after AKI *(2D)*.

6.2. Medication management following AKI and/or AKD

Recommendation 6.2.1: We recommend starting or resuming RASi in adults, unless there is a contraindication, in accordance with evidence-based guideline indications *(adults: 1B; children: 1D)*.

Practice Point 6.2.1: Evaluate the clinical indication for starting or resuming sodium-glucose cotransporter-2 inhibitors (SGLT2i), glucagon-like peptide-1 receptor agonists (GLP-1 RA) and mineralocorticoid receptor antagonists (MRA) in children and adults.

Practice Point 6.2.2: Assess the appropriateness of starting or resuming guideline-indicated medications at hospital discharge and by 3 months after AKI/AKD.

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Practice Point 6.2.3: Monitor RASi, MRA, or diuretic prescription and management following AKI/AKD in accordance with the KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease.

6.3 Evaluation for CKD

Practice Point 6.3.1: Assess kidney function and markers of kidney damage 3 months after AKI or AKD to evaluate for resolution, and new onset or worsening of preexisting CKD.

Practice Point 6.3.2: Serum cystatin C-based GFR estimation can be used to assess for CKD in children and adults after AKI in clinical situations where SCr is less accurate.

6.4 Post-discharge care for children and adults receiving RRT following AKI in the outpatient setting

Practice Point 6.4.1: RRT programs should incorporate comprehensive dialysis care and communication plans for children and adults receiving RRT following AKI tailored to their likelihood of dialysis liberation.

Practice Point 6.4.2: Engage patients, caregivers, and outpatient dialysis care teams in the development of a post-discharge care plan prior to transition from the hospital to community settings.

Practice Point 6.4.3: Dialysis care for children and adults receiving RRT following AKI requires clinical assessment of volume status, laboratory evaluation for evidence of kidney recovery, medication review and reconciliation, and patient education about identification of return of kidney function and minimizing kidney injury during the resolution phase.

Practice Point 6.4.4: Provide education and engage adults, children, and caregivers in shared decision-making focused around self-care, short- and long-term risks of permanent RRT and mortality, quality of life, and goals of care to inform decisions around dialysis care.

Practice Point 6.4.5: Upon discontinuation of outpatient dialysis, a nephrologist should conduct a comprehensive assessment within 7 days, followed by an additional evaluation of kidney function at 90 days.

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6.5. Considerations specific to children

6.5.1 Planning follow-up care for children after AKI and/or AKD

Practice Point 6.5.1.1: Assess children following AKI for global functional status at hospital discharge and for growth parameters and functional status at outpatient follow-up.

Practice Point 6.5.1.2: In children previously taking RASi, these medications should be resumed with resolution of AKI and/or AKD, unless there is a contraindication.

6.5.2. Post-discharge care for children receiving RRT following AKI in the outpatient setting

Practice Point 6.5.2.1: A risk-based approach guided by cause and severity of AKI and kidney health assessments at hospital discharge and one year following an AKI episode can be used to determine need for future nephrology follow-up in children.

Practice Point 6.5.2.2: Children recovering from AKI treated with RRT require individualized follow-up that includes age-appropriate functional and developmental assessments, growth and neurodevelopmental surveillance, and integrated care across nephrology, primary care, and relevant subspecialties.

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CHAPTER 1. AKI AND AKD DEFINITION, IDENTIFICATION, AND CLASSIFICATION

The definition of acute kidney impairment has evolved from a fragmented landscape of disparate terms into a unified framework of Acute Kidney Injury (AKI) and Acute Kidney Disease (AKD). While the field has relied on serum creatinine (SCr) and urine output since the standardization efforts of 2009, the shift toward consistent Kidney Disease: Improving Global Outcomes (KDIGO)-based staging has been instrumental in improving global epidemiological tracking and clinical risk stratification. However, as SCr often serves as a trailing marker of kinetic change, the current frontier of nephrology emphasizes integrating novel biomarkers and updated evidence to identify kidney stress earlier. This chapter explores the transition from these traditional functional markers to a modern, precision-based approach to diagnosis and classification.

1.1. Definition of AKI

Practice Point 1.1.1: Acute kidney injury (AKI) in children and adults is defined by the presence of one or more abnormalities of kidney function or structure known or presumed to have occurred within 7 days, in the appropriate clinical context (Table 1).

Table 1 | Criteria for acute kidney injury for children and adults (any one or more of the following within the corresponding time period)

Functional criteria	Structural criteria
• Increase in SCr by ≥0.3 mg/dl (≥26.5 μmol/l) within 48 hours • Increase in SCr by ≥1.5 times baseline that is known or presumed to have occurred within the prior 7 days • Increase in serum cystatin C by ≥1.5 times baseline that is known or presumed to have occurred within the prior 7 days • Mean urine volume of less than 0.5 ml/kg/h (based on ideal body weight) for ≥6 hours	• Elevation of a biomarker of kidney damage when used for its clinically validated and regulatory qualified indication, which is known or presumed to have occurred within the prior 7 days

SCr, serum creatinine

The KDIGO 2012 Clinical Practice Guideline for Acute Kidney Injury provided a definition for AKI based on changes in SCr and urine output that are associated with the risks of death and receipt of renal replacement therapy (RRT) in hospitalized patients.[1] SCr and urine output are markers of kidney function, specifically glomerular filtration rate (GFR). Both measures are widely used in routine clinical practice and can be obtained at relatively low cost. However, neither measure is entirely sensitive or specific to GFR and can lead to misclassification of AKI (Table 2).

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Table 2 | Limitations of SCr and urine output for the diagnosis of AKI

Traditional biomarker	Impact on AKI diagnosis
SCr concentration	
• Insensitive to kidney damage; nearly 50% of function must be lost before SCr increases	Delayed diagnosis
• Slow to increase following an insult (24-48 hours)	Delayed diagnosis
• Affected by liver function	Delayed/missed diagnosis
• Affected by muscle mass and metabolism	Delayed/missed diagnosis
• Affected by creatine intake	Erroneous diagnosis
• Small increases can occur due to physiological and analytic variability, particularly with low baseline glomerular filtration rate (e.g., CKD)	Erroneous diagnosis
• Increases without true reduction in glomerular filtration rate in the setting of o Hemoconcentration following diuresis o Inhibition of tubular secretion (e.g. medications like trimethoprim and cimetidine)	Erroneous diagnosis of AKI
• Physiological decrease during pregnancy	Delayed/missed diagnosis of AKI
• Increases in context of nephroprotective medications (i.e., RASi, SGLT2i)	Physiological hemodynamic adjustment misinterpreted as AKI
Urine output	
• Dependent on accurate measurement	Missed diagnosis
• Can be manipulated by diuretics	Delayed/missed diagnosis
• Oliguria may be physiological	Erroneous diagnosis

AKI, acute kidney injury; CKD, chronic kidney disease; RASi, renin-angiotensin inhibitors; SCr, serum creatinine; SGLT2i, sodium-glucose cotransporter-2 inhibitor

The development and validation of several novel biomarkers over the last decade has enabled earlier detection of kidney cellular stress, damage, or inflammation compared with the use of functional markers alone, thus enabling earlier intervention and potentially improving outcomes.[2] Further, alternative functional biomarkers (i.e., serum cystatin C) are now available that overcome some of the limitations of SCr. For instance, cystatin C is not confounded by muscle mass. However, these markers have their own limitations, as well (Recommendation 1.1.1).

The updated definition adds new criteria for the purpose of AKI detection based on abnormalities of kidney structure, which reflect cellular stress, damage, or inflammation that may occur in the presence or absence of reduced kidney function. These new structural criteria for AKI are intended to encompass a number of urine or serum biomarkers that have received regulatory qualification for use in specific clinical settings based in part on their ability to predict the development of AKI before functional criteria are met (Table 3 and 4).

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These biomarkers may become elevated before an increase in SCr or reduction in urine output occurs; a state that has previously been termed “subclinical AKI”. Examples of these biomarkers include urinary tissue inhibitor of metalloproteinases-2 (TIMP-2), insulin-like growth factor binding protein 7 (IGFBP7), neutrophil gelatinase-associated lipoprotein (NGAL), kidney injury molecule-1 (KIM-1), and liver-type fatty acid-binding protein (L-FABP).

A common method of categorizing kidney biomarkers is to stratify them based on their characteristics. Thus, some biomarkers primarily reflect glomerular filtration (i.e. serum cystatin C) whereas others represent tubular cell stress (i.e., IGFBP7 and TIMP-2) or tubular cell damage [i.e. NGAL, KIM-1, NAG, L-FABP]. Prolonged and increased expression of TIMP-2 and IGFBP7 may be synonymous with cell damage. Other kidney biomarkers indicate intrarenal inflammation (i.e. IL-18, IL-9, CCL14).

All biomarkers have specific characteristics, are released in response to particular triggers and have unique kinetic profiles, including half-life and time to peak value (Table 4). Many are elevated in AKI but also confounded by different medical conditions or interventions. Importantly, several studies in the literature used different cut-offs to distinguish between “biomarker-positive” versus “biomarker-negative” conditions, which explains some of the differences in performance but also makes direct comparisons between studies challenging.

It is important to keep these aspects in mind when measuring and interpreting biomarker values in specific patient cohorts. When deciding whether to integrate a biomarker into routine monitoring or to include a biomarker in the diagnostic work-up of a specific clinical setting, it is essential to select one that is physiologically and biologically relevant to the question of interest. Further, timing of measurement needs to be guided by the kinetic profile of the biomarker.

The availability and higher costs of new biomarker tests limit their use in many settings but it is possible that earlier detection of AKI may ultimately offset these costs due to lower resource utilization and healthcare spending.

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Table 3 | Select kidney biomarkers and reported clinical applications

Damage/stress biomarker	Outcome	Clinical application
Urinary [TIMP-2] * [IGFBP7][3]	Stage 2 or 3 AKI in critically ill patients	Cardiac surgery: PrevAKI RCT[4]: Application of a kidney care protocol to patients with elevated urinary [TIMP-2]*[IGFBP7] concentrations after cardiac surgery was associated with reduced incidence of AKI as defined by SCr criteria. PrevAKI-Multicenter RCT[2]: Application of a kidney care protocol to patients with elevated urinary [TIMP-2]*[IGFBP7] concentrations after cardiac surgery was associated with a reduced incidence of Stage 2–3 AKI as defined by SCr criteria. Major non-cardiac and cardiac surgery: BigpAK RCT[5, 6]: Application of a kidney care protocol to patients with elevated urinary [TIMP-2]*[IGFBP7] concentrations after major non-cardiac surgery was associated with a reduced incidence of Stage 2–3 AKI as defined by SCr criteria.
Urinary NGAL[7]	AKI Any AKI	A multicenter pooled analysis of prospective studies of patients with elevated urinary NGAL concentrations but not diagnosed as AKI by SCr (NGAL positive and SCr negative) showed worse outcomes such as dialysis requirement and in-hospital mortality compared with patients without elevated NGAL results and diagnosed as AKI by SCr (NGAL negative and SCr positive).[8] Systematic review and meta-analysis of 52 observational studies involving 13,040 patients reporting the performance of plasma and urinary NGAL concentrations in the setting of cardiac surgery, intensive care, or emergency department care showed that the AUCs for urinary NGAL were 0.74; 95% CI: 0.69–0.79, 0.73; 95% CI: 0.64–0.82, and 0.74; 95% CI: 0.66–0.82 for prediction of AKI, Stage 2–3 AKI, and AKI treated with RRT, respectively.[9]
Risk scores of granular/muddy brown casts	AKI	Among 197 patients with AKI, 79 experienced worsening of AKI from the time of nephrology consultation. The urinary sediment score predicted worsening of AKI due to acute tubular necrosis versus prerenal AKI during hospitalization.[10] Urine microscopy score was correlated with higher urine NGAL values and predictive of worsening AKI, both in sepsis-associated and non-associated AKI.[11]

AKI, acute kidney injury; AKI-D, acute kidney injury requiring dialysis; AUC, area under curve; BigpAK, Biomarker-guided intervention to prevent Acute Kidney Injury; IGFBP7, insulin-like growth factor binding protein 7; NGAL, neutrophil gelatinase-associated lipoprotein; PrevAKI, Prevention of Cardiac Surgery–Associated Acute Kidney Injury; RCT, randomized controlled trial; SCr, serum creatinine; TIMP-2, tissue inhibitor of metalloproteinases-2

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Table 4 | Description and characteristics of select AKI biomarkers as of November 2025

AKI biomarker	Characteristics	Biological sample	Intended use	Population/ settings studied	Half-life	Time to diagnostic value (i.e., timing of measurement)	Limitations/ confounders	Regulatory approval
Functional biomarkers								
Cystatin C	13 kDa cysteine protease inhibitor produced by nucleated human cells; freely filtered and completely reabsorbed and catabolized in healthy kidney tubular epithelial cells	Plasma	Diagnosis of AKI and marker of severity	ICU; liver transplantation; hospitalized patients	1.5–2 hours	12–24 hours	Elevated in CKD; confounded by age, sex, inflammatory state, diabetes, low albumin, glucocorticoids	U.S. FDA approved and CE-marked for GFR estimation in clinical practice
Proenkephalin A	Endogenous polypeptide hormone in adrenal medulla, immune system, and kidney tissue; freely filtered	Plasma	Diagnosis and assessment of AKI severity and kidney recovery	Hospitalized patients	Exact half-life not known; stable in blood up to 48 hours	Peak level at ~24 hours after kidney insult	Elevated in CKD; may be less sensitive than SCr or serum cystatin C	CE-marked for clinical use for kidney function assessment
Stress biomarkers								
Tissue metalloproteinase-2 (TIMP-2); Insulin-like growth factor binding protein 7 (IGFB7)	Proteins released by tubular epithelial cells (TIMP-2 distal tubule, IGFBP7 proximal tubule) that can induce cell cycle arrest	Urine	Prediction and diagnosis of AKI and assessment of severity	ICU	Exact half-life not known	4–5 hours	Significant decline in performance if measured beyond 12 hours after an AKI event	U.S. FDA and CE-marked for predicting Stage 2 or 3 AKI in adults
Damage biomarkers								

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AKI biomarker	Characteristics	Biological sample	Intended use	Population/ settings studied	Half-life	Time to diagnostic value (i.e., timing of measurement)	Limitations/ confounders	Regulatory approval
Dickkopf-3 (DKK3)	38kDa kidney tubular cell–derived glycoprotein; secreted into urine under tubular stress conditions	Urine	Risk assessment and prediction of AKI	Cardiac surgery	Variable half-life depending on clinical context	12–48 hours after the insult, depending on the type of kidney injury	Elevated in CKD	Not applicable
Alanine aminopeptidase (AAP); γ-glutamyl transpeptidase (γ-GT); Alkaline phosphatase (ALP)	Enzymes located in several organs, including the brush border of proximal tubular cells	Urine	Diagnosis and severity of AKI	ICU	Unknown	Within hours of kidney insult but varies depending on type of insult	Elevated in UTI, cardiovascular disease, stroke	Not applicable
C-C motif chemokine ligand 14 (CCL 14)	Pro-inflammatory chemokine implicated in tissue injury and repair processes; primarily produced by macrophages and monocytes; has a role in activating monocytes, recruiting immune cells to sites of injury / infection and in regulating inflammation in	Urine	Persistence of severe AKI	ICU	Not known	Within 36 hours of AKI onset	Confounded by comorbid conditions, including cancer and inflammation	CE-approved in Europe to predict persistent severe acute kidney injury

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AKI biomarker	Characteristics	Biological sample	Intended use	Population/ settings studied	Half-life	Time to diagnostic value (i.e., timing of measurement)	Limitations/ confounders	Regulatory approval
	various organ systems							
Chitinase 3-like protein 1	39 kDa intracellular protein of glycoside hydrolase family; expressed by endothelial cells, macrophages & neutrophils and released into the urine and plasma	Urine, plasma	Diagnosis of AKI	ICU	Unknown	Within 12–24 hours of kidney insult	Limited performance in real-world settings as a single biomarker; expression is strongly upregulated by various inflammatory and immunological diseases, including several cancers and atherosclerosis	Not applicable
Hepatocyte growth factor (HGF)	Antifibrotic cytokine produced by mesenchymal cells; involved in tubular cell regeneration after AKI and measured in plasma	Plasma	Severity of AKI and kidney recovery	Hospitalized	Short half-life (several minutes)	Variable; 4–12 hours after kidney insult depending on type of kidney insult	Decreased in anemia and increased in inflammatory state	Not applicable

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AKI biomarker	Characteristics	Biological sample	Intended use	Population/ settings studied	Half-life	Time to diagnostic value (i.e., timing of measurement)	Limitations/ confounders	Regulatory approval
Hepcidin	2.78 kDa peptide hormone predominantly produced in hepatocytes; freely filtered into urine and plasma	Urine, plasma	Diagnosis of AKI and assessment of severity	ICU	Short half-life (several minutes)	Variable; 4–12 hours after kidney insult depending on type of kidney insult	Decreased in anemia and increased in inflammatory state	Not applicable
Interleukin-18 (IL-18)	18 kDa pro-inflammatory cytokine; released into urine following tubular cell damage	Urine	Prediction and diagnosis of AKI	Hospitalized patients; patients in the emergency department	16 hours	Rise within 4–6 hours of kidney insult; peak at 12 hours	Elevated in inflammatory states	Not approved as AKI biomarker
Interleukin-9 (IL-9)	30-40kDa pleiotropic cytokine secreted by CD4+ helper cells	Urine	Differential diagnosis of AKI	Acute interstitial nephritis	Short half-life (few hours)	Prolonged time; not a marker of early AKI	Indicator of chronic changes; not indicator of early AKI	Not approved as AKI biomarker
Kidney injury molecule–1 (KIM-1)	Transmembrane glycoprotein produced by proximal tubular cell; released into urine after tubular cell damage	Urine	Prediction and diagnosis of AKI and assessment of severity	Hospitalized patients; patients in the emergency department	Varies with severity of kidney injury and other factors, including sepsis	12–24 hours after kidney insult	Mixed performance in chronic diseases, including immune diseases and cancer	FDA and EMA approved for preclinical drug development and monitoring of drug-induced kidney injury
Liver-type fatty acid-binding protein (L-FABP)	14 kDa intracellular lipid chaperone; freely filtered and reabsorbed in proximal tubule;	Urine; plasma	Diagnosis of AKI	ICU, patients in the emergency department	~75 hours	4–6 hours after kidney insult	Associated with anemia in people without diabetes	Approved for clinical use in Japan to measure tubular injury and

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AKI biomarker	Characteristics	Biological sample	Intended use	Population/ settings studied	Half-life	Time to diagnostic value (i.e., timing of measurement)	Limitations/ confounders	Regulatory approval
	excreted into urine after tubular cell damage and measured in the urine and plasma							predict kidney disease progression
N-acetyl-β-D-glucosaminidase (NAG)	>130 kDa lysosomal enzyme; released into urine after tubular damage	Urine	Diagnosis of AKI	Hospitalized patients	Intracellular half-life: 6 days; Half-life in urine: Not known	2–6 hours after kidney insult	Elevated in diabetes and albuminuria	Component of biomarker panel FDA qualitied for monitoring drug-induced kidney injury in early-phase clinical trials
Neutrophil gelatinase-associated lipocalin (NGAL)	≥3 different types measured in the urine and plasma: i.monomeric 25kDa glycoprotein produced by neutrophils and epithelial tissues, including tubular cells ii.homodimeric 45kDa protein produced by neutrophils iii.heterodimeric 135kDa protein	Urine; plasma	Diagnosis of AKI and measurement of severity	Hospitalized patients; patients in the emergency department	10–20 minutes	2-4 hours after kidney insult	Elevated in sepsis, UTI, CKD; measurement of general inflammation	FDA approved for identifying pediatric patients at risk of moderate-to-severe AKI

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AKI biomarker	Characteristics	Biological sample	Intended use	Population/ settings studied	Half-life	Time to diagnostic value (i.e., timing of measurement)	Limitations/ confounders	Regulatory approval
	produced by tubular cells							

AIN, acute interstitial nephritis; AKI, acute kidney injury; CE, European Conformity; CKD, chronic kidney disease; FDA, Food and Drug Administration; ICU, intensive care unit; RRT, renal replacement therapy; SCr, serum creatinine; U.S., United States; UTI, urinary tract infection

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Recommendation 1.1.1: We suggest using serum cystatin C to identify AKI in children and adults in clinical situations when serum creatinine (SCr) is less accurate *(2B)*.

This recommendation puts a high value on the greater sensitivity of cystatin C for detecting AKI in specific patient populations where changes in SCr can be insensitive. The recommendation places a lower value on resource use and additional costs. The feasibility of implementing this recommendation is highly dependent on the availability and turnaround time for cystatin C measurement.

Key information

Balance of benefits and harms

Previous AKI criteria using SCr and urine output measurements were established based on risks of kidney failure and mortality.[1, 12] Cystatin C is an alternative endogenous filtration marker that provides a more accurate GFR estimate than SCr in some specific populations. In a study of 38 mechanically ventilated adults in the intensive care unit (ICU), longer ICU stay was associated with greater differences between GFR estimated by serum cystatin C and SCr, suggesting that SCr can systematically overestimate GFR after prolonged critical illness.[13] A recent modeling study found that serum cystatin C can achieve steady-state concentration and meet AKI diagnostic thresholds significantly faster than SCr, with an advantage of 6–48 hours, depending on chronic kidney disease (CKD) severity. Serum cystatin C had greater sensitivity in detecting GFR reductions, with the ability to detect AKI within 12–24 hours after an insult, compared with 12–72 hours for SCr.[14]

Several meta-analyses have evaluated the diagnostic performance of cystatin C for early AKI identification. A meta-analysis by Lan *et al.* included 4 diagnostic accuracy studies that evaluated the performance of serum cystatin C, most often measured within 6–12 hours of major surgery in adults, using a reference standard of later development of AKI defined by Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE), Acute Kidney Injury Network (AKIN), or the KDIGO 2012 AKI criteria (Supplementary Tables S5).[15] Serum cystatin C exhibited relatively high discrimination with an area under the receiver-operating characteristics curve (AUROC) of 0.82 (95% confidence interval [CI]: 0.78–0.85). In an accompanying network meta-analysis, serum cystatin C exhibited the best discrimination and had the greatest specificity for early AKI detection among the 7 biomarkers included in the analysis.[15] Evidence review of 16 pediatric studies found that serum cystatin C had moderate accuracy to predict incident AKI (AUC 0.80) and moderate or severe AKI (AUC 0.83) in children (Supplementary Table S6).[16]

Certainty of evidence

In adults, there is moderate certainty of evidence that serum cystatin C has "moderate" accuracy as an early predictor of post-major surgery AKI, defined as an AUROC curve of between 0.75 and 0.85. The certainty of evidence was downgraded for some methodological limitations of the studies.

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In children, there is moderate certainty of evidence that serum cystatin C has "moderate" accuracy as an early predictor of incident AKI and Stage 2–3 AKI, defined as an AUROC of between 0.75 and 0.85. The certainty of evidence was downgraded for some methodological limitations of the studies, in addition to imprecision of the accuracy of Stage 2–3 AKI.

Values and preferences

This recommendation places a high value on the need for accurate and timely detection of a decline in GFR. The Work Group judged that healthcare professionals and most people at risk for AKI would prefer to use a more accurate test enabling earlier identification of AKI in situations where changes in SCr are insensitive or nonspecific. However, these benefits need to be balanced against the additional consequences and costs associated with cystatin C testing. The Work Group therefore prioritized reserving use of cystatin C for AKI detection to the clinical situations provided in Table 5 where more accurate measurement may alter clinical decisions.

Resource use and costs

Costs incurred for the higher frequency of cystatin C testing include one-time costs associated with initiation of the assay within a laboratory including building the information technology infrastructure and method verification studies; and continuous costs associated with consumables and maintaining the assay. If cystatin C is performed in an outside laboratory, other costs may ensue as with any laboratory test. Additional costs may also result from increased referrals to nephrologists to assist in interpretation of potentially discordant results between SCr and cystatin C results. Ideally, these costs would decrease over time with increased utilization and familiarity with the properties of the test.

Considerations for implementation

Implementation of this recommendation requires cystatin C testing be available in acute care centers with results available in a timely manner. Guidance to clinical laboratories on implementation and laboratory standards for cystatin C testing is provided in the KDIGO 2024 Clinical Practice Guideline for CKD (Practice Points 1.2.3.1 and 1.2.3.2).[17] Due to the increased costs of cystatin C testing, clear indications for testing with cystatin C in addition to SCr should be developed within institutions and SCr should remain the primary laboratory tests for AKI identification in the majority of patients. Education for healthcare professionals, caregivers, and people with AKI for optimal use and interpretation of cystatin C results is required.

Rationale

Changes in SCr may be insensitive for detection of AKI in acute and chronic illnesses that affect liver function and muscle mass (Table 2). In these scenarios, serum cystatin C may offer greater accuracy than SCr for early detection of AKI and opportunities for intervention.

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Potential harms include false positive test results, overdiagnosis, and the increased health care costs associated with the test itself as well as follow-up testing. In addition, discordant results between SCr and cystatin C may lead to increased nephrology consultations. Obtaining cystatin C results may take longer than SCr result depending on the local laboratory infrastructure and processes, which may lead to delays in recognition and offset the benefits of its use if results are not reported in a timely manner. Table 5 outlines specific situations where cystatin C measurement may be preferable to SCr to detect reduced GFR.

Table 5. Specific situations where serum cystatin C measurement may be preferable to SCr to detect reduced GFR

Domain	Specific clinical condition
Changes in muscle mass	Muscle wasting after prolonged illness Neurological diseases (e.g., muscle dystrophy) Spinal cord injury, paraplegia/quadriplegia Above knee amputation Extreme sport/exercise Eating disorders
Diet	Low-protein diet Vegetarian High protein diets and creatine supplementation
Medications	Drugs that interfere with tubular secretion of creatinine (e.g., cimetidine, trimethoprim)

GFR, glomerular filtration rate; SCr, serum creatinine

Practice Point 1.1.2: A baseline SCr value should be ascertained for all patients with suspected or confirmed AKI.

The KDIGO SCr criteria for AKI are based on an increase from a baseline value known or presumed to have occurred over a short time frame. Identification of an accurate baseline value is therefore required to establish whether a specific SCr value represents a change and whether the change is sufficient to meet AKI criteria. This is also needed for staging the severity of AKI based on the magnitude of SCr increase and for ascertaining the extent of recovery of GFR following AKI. A baseline SCr should be representative of a patient's GFR before the onset of AKI. In clinical practice, variation in the extent of SCr testing for a patient will influence the selection of a representative SCr value as the baseline value. Access to previous laboratory results obtained prior to an acute illness is helpful in establishing an appropriate baseline. In their absence, several approaches have been recommended in the literature including use of a SCr representative of normal GFR for a patient's age and sex, or the use of a subsequent lower SCr value when SCr values are declining in the absence of RRT.

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Practice Point 1.1.3: In adults, select the baseline SCr or cystatin C for an AKI episode using a hierarchical approach (Figure 1).

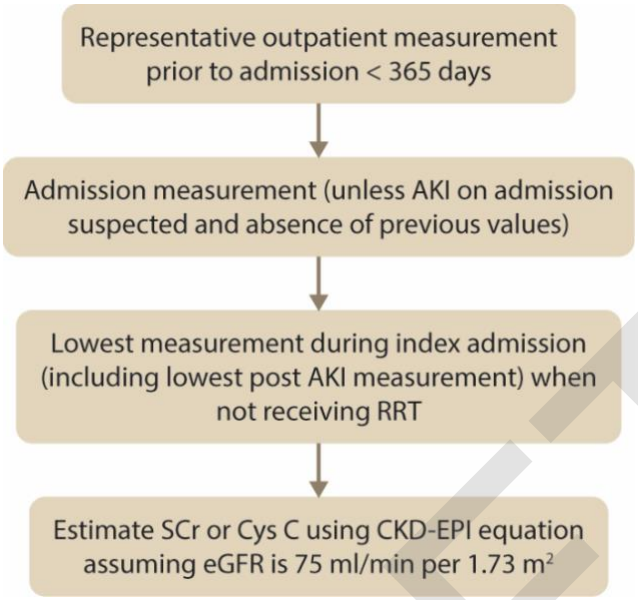
Representative outpatient measurement prior to admission < 365 days
Admission measurement (unless AKI on admission suspected and absence of previous values)
Lowest measurement during index admission (including lowest post AKI measurement) when not receiving RRT
Estimate SCr or Cys C using CKD-EPI equation assuming eGFR is 75 ml/min per 1.73 m²

Figure 1 | Hierarchical approach to the selection of the baseline SCr value used to characterize an AKI event in adults*. *A representative primary care/outpatient serum creatinine (SCr) should ideally reflect the stable clinical state, and may be a mean, median, or most recent value between 8–365 days before a hospital admission (or acute event). AKI, acute kidney injury; Cys C, cystatin C; eGFR, estimated glomerular filtration rate; RRT, renal replacement therapy

There are several different approaches described for ascertaining baseline SCr values (Supplementary Tables S7 and S8). Therefore, we advise using a mean, median, or most recent SCr measurement between 8–365 days prior to admission or acute event as the preferred method to establish baseline kidney function representing a stable clinical state. Differences in methods for establishing baseline SCr can affect whether patients meet AKI criteria leading to both over- and underdiagnosis. Underdiagnosis of AKI can lead to delayed recognition thereby delaying investigations and treatment. Overdiagnosis of AKI in people with CKD may expose patients to unwarranted tests and interventions. In addition, use of varying methods in epidemiological studies impacts the comparability of findings, limiting interpretation of consistency of findings across different geographic regions and clinical settings.

Access to outpatient SCr values may not be available in some settings. Wherever possible, systems should ideally be integrated or if this is not possible, primary care and outpatient values should be accessible to clinicians in secondary care settings, and vice versa. Education of healthcare professionals is required to ensure optimum implementation of this recommendation.

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In the absence of an available outpatient SCr within the last year, we advise using SCr on admission as the next option unless AKI is suspected on admission (e.g., community-acquired AKI). This provides a readily available value that is more appropriate for patients admitted for elective procedures (e.g., surgery, imaging procedures) but may be affected by conditions which have precipitated nonelective admission for conditions such as volume depletion or sepsis. An alternative to this approach is the use of the minimum value during admission including post-AKI values, allowing for retrospective AKI diagnosis. This approach is less desirable due to the influence of fluctuations or interventions that might lower SCr, such as fluid administration or withdrawal of medications that lower GFR and would not be representative of the true baseline in patients who have not fully recovered kidney function.

In the absence of any available measurements, we advise back calculating, assuming an estimated GFR (eGFR) of 75 ml/min per 1.73 m^2 for adults, based on a validated eGFR estimating equation is acceptable.[18] Use of an equation with greater accuracy at higher eGFR, such as the Chronic Kidney Disease Epidemiology Collaboration Equation (CKD EPI) equation, is preferable to equations that have been previously recommended such as the Modification of Diet in Renal Disease (MDRD) equation. However, assuming a baseline GFR of 75 ml/min per 1.73 m^2 for adults does not account for individual patient characteristics and the presence of underlying CKD. Studies have shown that this method leads to both over- and underestimation of AKI.[19-24] Approaches specific to calculating a baseline SCr in children are discussed in Practice Point 1.6.2.

For the purpose of epidemiological research, use the median of outpatient values 7–365 days prior to admission or an acute event is advised. It is important to ensure that there is a uniform approach to defining AKI for epidemiological studies, allowing for valid comparisons between studies and for analyses of trends over time.

1.2. Staging of AKI

Practice Point 1.2.1: The severity of AKI in children and adults is staged according to individual components or combinations of the following SCr and urine output criteria and presence or absence of an elevated biomarker of kidney stress or damage (Table 6).

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Table 6 | Severity staging system for AKI

Functional criteria				Structural criteria	
Serum creatinine		Urine output		Damage biomarker	
Stage	**Criteria**	**Stage**	**Criteria**	**Stage**	**Criteria**
C0		**U0**		**B1**	**Positive**
C1	≥0.3 mg/dl (≥26.5 µmol/l) increase, *Or* 1.5-1.9 times baseline	**U1**	<0.5 ml/kg/h for 6–12 hours	**B0**	Negative
				B1	Positive
C2	2–2.9 times baseline	**U2**	<0.5 ml/kg/h for >12 hours	**B0**	Negative
				B1	Positive
C3	≥3.0 times baseline, *Or* Increase in SCr to ≥4.0 mg/dl (≥353.6 µmol/l) *Or* Initiation of RRT	**U3**	<0.3 ml/kg/h for >24 hours or anuria for >12 hours	**B0**	Negative
				B1	Positive

*C1-C3 indicates acute kidney injury (AKI) severity stage according to serum creatinine (SCr) criteria, U1-U3 indicates AKI severity stage according to urine output criteria, B0/B1 indicates staging by absence or presence of an elevated damage biomarker. Relevant components of the staging system can be employed to classify the severity of AKI according to the measurements collected for an individual. RRT, renal replacement therapy

The KDIGO 2012 AKI staging system was based on SCr and urine output criteria with the patient assigned a severity Stage (1–3) according to the highest (worst) SCr or urine output stage. Subsequently, numerous large observational studies from intensive care settings have shown poor agreement and varying prognosis between SCr and urine output criteria for identifying and staging AKI (Supplementary Tables S9 and S10). Kellum *et al.* examined outcomes of 32,045 patients from 8 adult ICUs in the U.S. with electronic records of SCr and urine output measures and showed that, across the KDIGO 2012 AKI stages based on SCr, higher stages of urine output criteria were generally associated with higher risks of both hospital mortality and RRT.[25] A subsequent study restricted to adults who received cardiac surgery found that major adverse kidney events (MAKE) at 180 days after surgery (defined by death, RRT, or persistent abnormal kidney function) also increased with both higher SCr and urine output stages.[26] In a study by Bianchi *et al*., examining the KDIGO 2012 criteria in an adult ICU in Switzerland, urine output identified AKI in patients who did not fulfill SCr criteria or increased their AKI stage in 8073 (51.7%) patients with AKI.[27, 28] This included 2443 (30.2%) patients whose AKI severity stage was increased by adding urine output criteria. This reclassification of the AKI stage with the addition of urine output to SCr criteria had important prognostic implications, as 90-day mortality varied by urine output category within each SCr category. In multivariable adjusted models, greater urine output stages were

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associated with a significantly higher 90-day mortality within each SCr stage; for example, among patients with Stage 1 AKI based on SCr, those with Stage 3, 2, 1 and no AKI based on urine output criteria had 90-day mortality risks of 37%, 17%, 16%, and 11%, respectively. Additional studies have demonstrated that the addition of the urine output criteria to the SCr criteria further stratifies patients for risk of adverse patient outcomes[25, 26, 28-30]

Recently, alternative urine output criteria based on modified thresholds for urine output staging have been proposed (Supplementary Tables S11 and S12). Machado *et al.* compared the sensitivity and specificity of different urine thresholds and time frames for mortality prediction in critically ill adults.[31] They selected 3 cut-off points for alternative urine output staging: Stage 1 (0.2–0.3 ml/kg/h), Stage 2 (0.1–0.2 ml/kg/h), and Stage 3 (<0.1 ml/kg/h), all over 6 hours. When combined with KDIGO SCr criteria, this alternative staging system exhibited better discrimination, with net improvement in risk classification compared with the KDIGO 2012 urine output and SCr criteria for predicting mortality. This suggests that lower urine thresholds within 6 hours are prognostically important in critically ill adults but further research is needed.

The inclusion of structural criteria for AKI based on elevation of damage biomarkers has been shown to further improve the classification and prognostic risk stratification of AKI beyond that provided by SCr alone. A pooled analysis of critically ill patients from 10 observational studies reported that, among patients meeting SCr criteria for AKI, the subsequent risk of RRT initiation, length of ICU and hospital stay, and in-hospital mortality were greater in NGAL-positive compared with NGAL-negative patients.[32] In a study of adult patients receiving mechanical ventilation, SCr combined with urinary NGAL provided a more accurate prediction of RRT requirement than SCr or NGAL alone.[33] Another structural biomarker, CCL14, has been shown to identify patients at higher risk of persistent (≥72 hours) Stage 3 AKI in critically ill patients meeting KDIGO 2012 Stage 2 or 3 AKI criteria.[34]

The updated staging system for AKI presented here incorporates both functional (SCr, and urine output) in addition to structural criteria (damage biomarkers) to stage the severity of AKI and to improve risk stratification for important clinical outcomes of AKI. Although measurement of SCr is routinely performed in many acute care settings, accurate measurement of urine output is not feasible in all clinical settings which limits accurate staging of patients outside intensive care units and for patients without urinary catheters.

This revised staging system places a high value on more granular evaluation of AKI severity based on prognosis. However, new damage biomarker tests are more expensive and availability is limited in both high and low resource settings. Nonetheless, relevant components of the staging system can be employed to classify the severity of AKI according to the measurements available in a given institution.

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Practice Point 1.2.2: Transient AKI is differentiated from persistent AKI based on an increase in SCr or cystatin C or decrease in urine output lasting ≤48 versus >48 hours (Table 7).

Table 7 | Definitions of transient and persistent AKI

	Duration of reduction in kidney function
Transient AKI	≤48 hour increase in SCr or cystatin C or reduced urine output
Persistent AKI	>48 hour and up to 7 days increase in SCr or cystatin C or reduced urine output

AKI, acute kidney injury; SCr, serum creatinine

Since publication of the KDIGO 2012 AKI guideline, there have been variations in how the trajectory of kidney function, resolution, and transient versus persistent AKI have been defined (Supplementary Tables S13 and S14). Transient AKI has typically been defined by a return of SCr to baseline levels within 48–72 hours. Studies of AKI resolution patterns have consistently demonstrated that complete and sustained reversal of AKI within this timeframe is associated with better long-term outcomes.[35-57] This may reflect the fact that transient AKI is often caused by reduced kidney perfusion, and that correction of kidney perfusion, such as by correcting volume status or removing medications that lower glomerular pressure, can rapidly restore kidney function to baseline levels. In 2017, the Acute Disease Quality Initiative (ADQI) group recommended defining transient or rapid reversal of AKI as within 48 hours of onset and persistent AKI as beyond 48 hours.[58] Jensen *et al*. showed in a large population-based cohort that, compared to transient AKI (≤48 hours), persistent AKI (2–7 days) was associated with a higher incidence of CKD and kidney failure.[44] Analysis of a large cohort of hospitalized patients showed that mortality was higher in those with persistent AKI compared with transient AKI defined as reversal within 48 hours.[40] A cohort study from the Veterans Health Administration in the U.S. demonstrated a >40% increase in risk of CKD G3 or higher following transient AKI lasting less than 2 days, compared to a 2-fold increase in risk among those with AKI whose kidney function recovered to within 0.3 mg/dl of baseline SCr within 3–10 days.[57] Distinguishing persistent versus transient AKI is thus relevant to assessing the long-term risk of CKD, kidney failure, and survival after AKI, with implications for subsequent lab testing and follow-up of people with AKI. Standardizing the definition for transient and persistent AKI is important to enable consistent communication about the trajectory of AKI and for comparison of both epidemiological and clinical studies.

The Work Group favored the adoption of a 48-hour time frame as opposed to the 72-hour time frame because i) an earlier assessment of kidney function after onset of AKI was felt to be most clinically appropriate, and ii) it reflects the definitions used in the majority of the available evidence and the consistency of relationships with CKD and mortality across studies. Although most studies have defined transient versus persistent AKI on the basis of SCr alone, the Work Group felt it was appropriate to also apply this timeframe to other

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functional criteria for AKI, including serum cystatin C and urine output. This definition applies to both children and adults.

Practice Point 1.2.3: The underlying cause of AKI should be identified based on susceptibilities and exposures, clinical context, history and physical examination, and appropriate diagnostic laboratory and imaging testing to inform specific management.

AKI is a heterogeneous clinical syndrome with many etiologies, which vary in frequency by clinical setting and their responsiveness to general supportive care of the acutely ill patient. Some causes of AKI require specific treatments, including acute glomerulonephritis, vasculitis, interstitial nephritis, thrombotic microangiopathy, and urinary tract obstruction (Table 8). In some patients, AKI is part of a systemic illness, such as myeloma or connective tissue disease where AKI may improve with treatment of the underlying condition. The clinical evaluation of AKI includes a careful history and physical examination to identify exposures and susceptibilities and guide appropriate laboratory and imaging tests.

Important exposures include dehydration, infections, trauma, burns, surgery, shock, drugs, poisons, and toxins. Susceptibilities to AKI following these exposures can vary between individuals on the basis of age, sex, race and comorbidities such as CKD, diabetes mellitus, cancer, heart, lung, and liver disease.

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Table 8 | Causes of AKI requiring specific treatments to protect the kidney

Causes	Diagnostic tests	Therapeutic managements
Reduction of renal perfusion	Evaluation of intravascular volume and cardiac function, urinary diagnostic indices (e.g., fractional excretion of sodium or urea)	Stabilize and optimize renal perfusion; fluids/vasopressors for volume depletion/shock. Decongestion for right heart failure, relief of elevated intraabdominal pressure.
Acute glomerulonephritis, vasculitis, thrombotic microangiopathy	Urine sediment analysis, serologic testing, hematologic testing, kidney biopsy	Steroids, immunosuppressive therapy, plasma exchange, discontinuation of causative agents
Urinary tract obstruction	Kidney imaging (ultrasound or CT)	Urological/radiological intervention for release of obstruction
Acute interstitial nephritis	Urinalysis and microscopy; kidney biopsy; eosinophilia	Discontinuation of offending trigger/substance; consideration of steroid therapy
Hepatorenal syndrome	Evaluation of effective blood volume and portal hypertension; urine sodium, urine NGAL	Vasoconstrictive agents (e.g., terlipressin), liver transplantation
Multiple myeloma	Abnormal monoclonal proteins (M proteins) and free light chains in blood and urine, kidney biopsy	Reducing light chains by hydration, chemotherapy ± plasmapheresis
Rhabdomyolysis	Increased creatinine kinase and myoglobin in blood and/or urine; positive hematuria with no RBC in urine sediment with	Fluid therapy
Tumor lysis syndrome	LDH, uric acid, serum calcium, serum phosphate	Xanthine oxidase inhibitor to reduce uric acid production

AKI, acute kidney injury; CT, computed tomography; LDH, lactate dehydrogenase; NGAL, neutrophil gelatinase-associated lipocalin

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1.3. Definition of AKD

Practice Point 1.3.1: Acute kidney disease (AKD) in children and adults is defined as the presence of any of the following functional or structural criteria in the appropriate clinical context with a duration ≤3 months (Table 9).

Table 9 | Criteria for AKD (any one or more of the following with a duration ≤3 months)

Functional criteria	Structural criteria
AKI (by functional criteria), *Or* GFR <60 ml/min per 1.73 m^2* *Or* Decrease in GFR by ≥35 ml/min per 1.73 m^2 from baseline *Or* Increase in SCr by >50%	AKI (by structural criteria) *Or* Marker of kidney damage (albuminuria, hematuria, or leukocyturia are most common)

*GFR <60 ml/min per 1.73 m^2 criterion does not apply to children younger than 2 years old. AKI, acute kidney disease; AKI, acute kidney injury; GFR, glomerular filtration rate; SCr, serum creatinine

AKD includes AKI as well as alterations of kidney function and structure with a duration ≤3 months. Patients with AKD may not meet the criteria for AKI because the GFR decline is not sufficient to fulfill criteria for AKI (i.e., GFR decline is too small or too slow). Recognizing AKD enables an integrated clinical approach to people with abnormalities of kidney function and structure, including alterations of kidney function and structure that do not meet the criteria for the definition of either AKI or CKD, yet may need medical attention to restore kidney function and reverse damage to kidney structure to avoid adverse outcomes. AKD is nearly 3 times as prevalent as AKI (Figure 2).[59] The association between AKD and adverse patient outcomes has been well-established with many observational studies showing that AKD without AKI is associated with CKD, requirement for RRT, MAKE, length of hospital stay, and mortality (Supplementary Table S15). This definition applies to both children and adults.

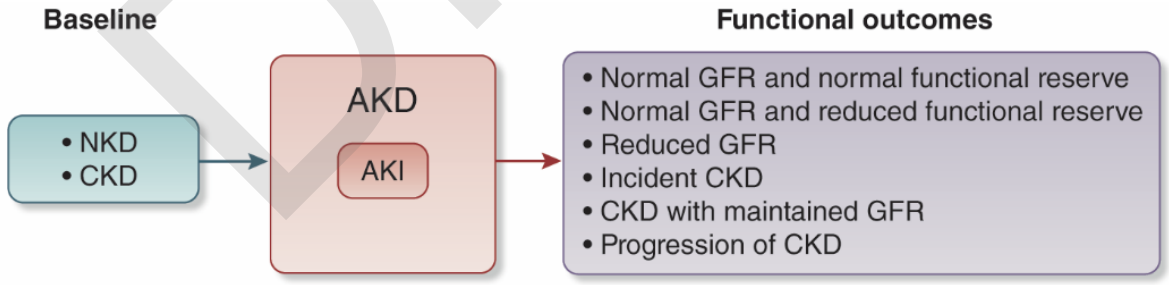

Figure 2 | AKD, AKI, and kidney disease outcomes. AKD, acute kidney disease; AKI, acute kidney injury; CKD, chronic kidney disease; GFR, glomerular filtration rate; NKD, no kidney disease

A recent systematic review on the incidence of AKD and its associated adverse outcomes included 59 studies involving almost 6 million participants.[60] The authors included studies defining AKD by the KDIGO definition. The pooled incidence of AKD defined by

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the KDIGO criteria was 11.1% (95% CI: 7.6%–16.3%). Among studies that were not restricted only to patients with AKI at study entry, AKD incidence was similar at 11.1% and the pooled odds ratio (OR) of all-cause mortality associated with AKD was 3.8 (95% CI: 2.2–6.7).

Recognition of AKD across healthcare settings identifies patients with kidney disease at risk of adverse long-term kidney and related outcomes, such as cardiovascular events and mortality. There may be a risk of misdiagnosing CKD as AKD when prior testing has not been performed, leading to unnecessary interventions and anxiety. Increased testing may place an additional burden on healthcare systems and there also may be variability in interpretation and management. However, earlier identification and management of AKD may reduce longer term costs associated with CKD such as the requirement for RRT and cardiovascular complications. Education and training of healthcare professionals on interpretation of this definition is required, particularly in primary care as it is more commonly encountered in the outpatient setting, and healthcare professionals may be less familiar with management approaches for AKD than CKD. Where possible, integration into electronic health care record systems and decision support tools may assist the implementation.

Practice Point 1.3.2: AKD without AKI should be differentiated from AKD following AKI because the underlying causes and clinical management can be different.

The diseases and disorders that cause AKI can impact long-term kidney function and so AKD may be present following AKI, with the risk varying according to AKI severity and preexisting CKD. Patients can also be identified with AKD without meeting criteria for AKI. In these patients, changes in kidney function and structure are not of sufficient magnitude or identified rapidly enough to meet AKI criteria yet have been shown to be prognostically important.

A cohort study of 1.1 million adult Canadian residents concluded that AKD without AKI was 3 times more common than AKI, and was more often identified on outpatient rather than inpatient SCr and albuminuria testing.[61] AKD without AKI was significantly associated with an increased risk for mortality and RRT requirement in comparison with no kidney disease. However, the multivariable-adjusted hazard ratio (HR) of mortality for AKD without AKI was lower than for AKI. AKD without AKI was also associated with a higher risk of new onset CKD than AKI among patients without preexisting CKD. In a cohort of over 5900 critically ill pediatric patients with preserved baseline kidney function, AKD without AKI was independently associated with a >7-fold increased odds of MAKE at 90 days ($MAKE_{90}$), including persistent abnormal kidney function, dialysis, or death, compared to those with no AKD (adjusted OR: 7.83; 95% CI: 4.54–13.51).[62]

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AKD without AKI is often seen in community or primary care settings and has been described in populations with liver cirrhosis,[63, 64] acute decompensated heart failure,[65] and among patients who received a kidney biopsy, including those with biopsy-proven crescentic glomerulonephritis.[66] AKD without AKI likely identifies patients with a distinct distribution of etiologies of kidney disease and concomitant risk of adverse outcomes, which may warrant different clinical management strategies to those with AKD following AKI.

1.4. AKI and AKD resolution

Practice Point 1.4.1: Complete and partial resolution of AKI and AKD are defined by changes in SCr, serum cystatin C, or estimated glomerular filtration rate (eGFR) as shown in Table 10.

Table 10 | Criteria for resolution of AKI and AKD

	Complete resolution	Partial resolution
AKI	SCr or serum cystatin C <1.2 times higher than baseline within 7 days	SCr or serum cystatin C ≥1.2 to <1.5 times higher than baseline within 7 days
AKD	SCr or serum cystatin C <1.2 times higher than baseline, *Or* eGFR ≥80% of baseline within 3 months	SCr or serum cystatin C ≥1.2 to <1.5 times higher than baseline, *Or* eGFR <80% to >66% of baseline within 3 months

AKD, acute kidney disease; AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; SCr, serum creatinine

Although many studies have evaluated the relationships between recovery of kidney function based on SCr values and patient outcomes, inconsistent definitions have been used for resolution of AKI and AKD[67] and considerable variation of the criteria is applied in the published literature.[38, 51, 52, 54, 56, 57, 68, 69] A standardized definition in children and adults is important for both clinical practice and research. Firstly, a lack of a standard definition results in variations of interpretation by healthcare professionals which leads to inconsistent decision-making around different aspects of clinical care such as follow-up planning and resource allocation. Secondly, identifying partial resolution can allow for earlier interventions with the potential to mitigate the AKI to CKD transition and thus improve kidney outcomes. Thirdly, a standardized definition would allow for comparison across studies and is vital for clinical trial design as well as for validation of biomarkers that predict resolution versus nonresolution.

The Work Group judged that a return of SCr to <1.2 times higher than baseline indicates return of GFR to baseline for most patients, allowing for non-clinically significant fluctuations in SCr. The prognostic relevance of this definition is supported by several studies. Pannu *et al*. examined different percentage changes in SCr from baseline to define recovery of kidney function in a population-based cohort in Alberta, Canada.[54] There was a significantly higher risk for mortality and adverse kidney outcomes among patients with AKI and a SCr that remained 25% above baseline at 90 days after AKI onset. In a population-

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based cohort from Scotland, Sawhney *et al.* defined complete resolution of AKI by the last SCr <1.2 times higher than baseline SCr and partial resolution of AKI as the last SCr ≥1.2 to <1.5 times higher than baseline within 7 of AKI onset. The percentage of patients without subsequent kidney recovery by 90 days was 3.5% among those with complete resolution, 10.4% among those with partial resolution, and 30.1% without partial or complete resolution.[69]

By definition, patients with AKI who do not recover kidney function by 7 days are deemed to have AKD which can last for up to 3 months. Resolution of AKD should be determined before 3 months since closer clinical assessment to identify and address factors that may cause ongoing kidney injury and mediate AKD to CKD transition may be warranted. Beyond 3 months, patients without resolution of AKD meet the criteria for CKD and should be described as having CKD and a history of AKD (Section 6.3). Large population-based studies have examined the prognosis of AKD according to SCr recovery status within 3 months of AKI onset.[38, 68] These studies have demonstrated that people with AKD are at increased risk for development of new onset CKD as well as progression of preexisting CKD.[38, 61] People not meeting criteria for CKD after the period of AKD should be described as having a history of AKD and can be further distinguished as having partial or complete resolution of AKD, to further identify their increased risk for new onset or progression of CKD.

1.5. Recurrent AKI

Practice Point 1.5.1: Recurrent AKI is defined as a new episode of AKI occurring after partial or complete resolution from a previous episode of AKI.

Recurrent AKI is associated with adverse outcomes.[46, 50, 55] However, there is considerable variation in how recurrent AKI has been defined previously. Liu *et al.* defined recurrent AKI in adults as being rehospitalized with a SCr level increase by ≥0.3 mg/dl within 48 hours of readmission or ≥50% above a "baseline" SCr level.[55] Walker *et al*. defined recurrent AKI as meeting the biochemical definition of AKI within the observation period of 6 years[50] and Altawalbeh *et al*., within 5 years.[46]

In the Assessment of Worldwide Acute Kidney injury Epidemiology in Neonates (AWAKEN) cohort study of 2162 critically ill neonates, recurrent AKI was defined as a new AKI episode occurring only after SCr had returned to the prior baseline.[36] Among neonates with AKI, 22% experienced recurrent AKI. These infants had significantly longer hospital stays than those with a single episode of AKI (median 60 vs. 18 days). Recurrent AKI was also independently associated with reduced likelihood of discharge (adjusted HR: 0.7; 95% CI: 0.6–0.9). Similarly, in a retrospective cohort of preterm neonates ≤28 weeks gestation, Adegboyega *et al*. found that 24% developed recurrent AKI.[47] Early-onset and severe initial AKI were associated with increased risk for recurrent AKI, which in turn was linked with a

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significantly longer hospital stay (+36 days) and increased mortality (adjusted OR: 4.55; 95% CI: 1.12–18.51) compared to a single episode of AKI.

The Work Group deemed that the definition of recurrent AKI be consistent with the proposed resolution definition (Table 10), so that each episode of AKI is identified as a separate event, based on a new baseline SCr or cystatin C where warranted, without imposing a timeframe between a first and subsequent AKI episode. A standardized definition will allow for comparison of predictors, incidence, and prognosis across studies, and could aid in distinguishing patients with new episodes warranting assessment from those with sequelae of AKD or CKD.

1.6. Considerations specific to children

1.6.1. Definition of AKI

Practice Point 1.6.1.1: Age specific references ranges should be used when serum cystatin C is used to detect AKI in children.

In children, like adults, AKI is defined by functional and structural criteria (Table 1). Serum cystatin C as an alternative marker of kidney function that has robust evidence of performance in children across diverse clinical settings, including critical illness, septic shock, cardiac surgery, and liver disease with strong diagnostic performance for early AKI detection. However, cystatin C levels are influenced by age, with known elevations during infancy and changes in adolescence due to developmental changes. Therefore, age-specific reference ranges are essential for accurate interpretation, particularly when using cystatin C to detect AKI in neonates. Serum cystatin C levels vary significantly during puberty: median concentrations increase in boys (to approximately 0.98 mg/l) and decrease in girls (to around 0.86 mg/l) between ages 11 and 14. These changes strongly correlate with Tanner stage ($\beta = +0.105$ mg/l per stage in males and $\beta = -0.093$ mg/l in females, both $p < 0.01$).[70]

1.6.2. Determination of baseline kidney function

Practice Point 1.6.2.1: In children (except neonates), select the baseline SCr or serum cystatin C for an AKI episode using a hierarchical approach (Figure 3).

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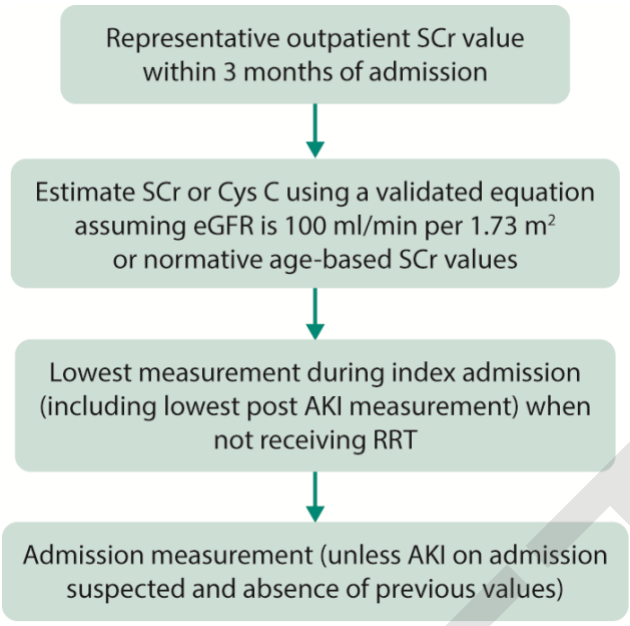
Representative outpatient SCr value within 3 months of admission
Estimate SCr or Cys C using a validated equation assuming eGFR is 100 ml/min per 1.73 m²
or normative age-based SCr values
Lowest measurement during index admission (including lowest post AKI measurement) when not receiving RRT
Admission measurement (unless AKI on admission suspected and absence of previous values)

Figure 3 | Hierarchical approach to the selection of the baseline SCr value used to characterize an AKI event in children*. *A representative outpatient SCr should ideally reflect the mean, median, or most recent value within 3 months of admission or acute event. AKI, acute kidney injury; Cys C, cystatin C; eGFR, estimated glomerular filtration rate; RRT, renal replacement therapy; SCr, serum creatinine

In children, defining baseline SCr for AKI diagnosis requires an approach that prioritizes outpatient values obtained within the past 3 months, recognizing that kidney function changes more dynamically in children than in adults.[71] However, access to outpatient SCr values may not be available in some settings. Wherever possible, systems should ideally be integrated or if this is not possible, outpatient values should be accessible to clinicians in secondary care settings. Education of healthcare professionals is required to ensure optimum implementation of this recommendation.

When such values are unavailable or not appropriate, it is reasonable to use equations such as the age-based creatinine and age-based creatinine with recovery equations, which were derived from a large cohort of hospitalized children without known CKD (Table 11).[72, 73] However, they have important limitations.

When no prior values are available, using the admission SCr may be acceptable with caution, although this approach risks underrecognizing AKI in children who present with early kidney injury.

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Table 11 | Baseline creatinine estimation methods in children

Method	Description	Strengths	Limitations	Best use context
Known baseline SCr	Previous outpatient or pre-illness SCr value from medical records in the past 3 months in children	Most accurate if GFR measured prior to acute illness	Often unavailable in acute settings; may not reflect current status if outdated	When prior measurements are available in the absence of acute illness
Back-calculation using a validated GFR estimating equation	Use of the Schwartz equation for children, incorporating height to calculate SCr, assuming an eGFR of 100–120 ml/min per 1.73 m²	More accurate estimate of eGFR at higher GFRs; assumes no CKD	Assumes no preexisting CKD	When no prior or subsequent lower SCr measurement are available
		Widely validated and standard in pediatric AKI research; accounts for body size	Overestimates GFR in infants or underweight children; assumes fixed GFR	When height is available
	Use of the Pottel (Q-age) equation for children, without need for height or weight to back calculate SCr assuming a GFR of 120 ml/min per 1.73 m²	Does not require height; useful in low-resource settings	Less accurate in children with atypical growth or development	In settings lacking height measurements or in lean/malnourished children
Normative age-based SCr values	Uses population normative SCr ranges by age and sex from healthy children	Quick and easy when height is unavailable	May misclassify AKI due to inter-individual variability; not personalized	When no other measurements are available
Nadir SCr (lowest during hospitalization)	Uses lowest measured SCr during hospital stay	Reflects individual patient's physiology; better in patients with serial SCr measurement	Not useful early in hospitalized children; may underestimate if resolution is incomplete or in critical illness with augmented clearance or decreased creatine production	In acute care settings with multiple measurements and no known preadmission values

AKI, acute kidney injury; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; SCr, serum creatinine

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Practice Point 1.6.2.2: In children, specific considerations related to age are needed when determining a baseline SCr.

In pediatric studies, eGFR values are typically reported within the range of 100–120 ml/min per 1.73 m² and not all equations to determine baseline SCr consider patient age (Table 10). For instance, back-calculating baseline SCr using a fixed eGFR of 100–120 ml/min per 1.73 m^2 with the Schwartz equation has been shown to be particularly inaccurate in children under 2 years of age, where kidney function is physiologically lower and more variable. [74] Although using an assumed eGFR of 120 ml/min per 1.73 m² tends to produce lower bias with about 25% absolute error, opting for 100 ml/min per 1.73 m² may provide a more conservative estimate to minimize the risk of overestimating AKI.[75]

In younger children, the use of age-based normative GFR values substantially improves the accuracy and agreement of the estimated baseline SCr. Height-dependent equations may not be feasible in hospitalized children because height is often missing or unreliable in health records during acute illnesses.

Differences in methods for establishing baseline kidney function can affect whether patients meet AKI criteria leading to both over- and underdiagnosis. Underdiagnosis of AKI can lead to delayed recognition thereby delaying investigations and treatment. Overdiagnosis of AKI in people with CKD may expose patients to unwarranted tests and interventions. In addition, use of varying methods in epidemiological studies impacts the comparability of findings, limiting interpretation of consistency of findings across different geographic regions and clinical settings.

1.6.3. Criteria for neonatal AKI

Practice Point 1.6.3.1: The criteria for neonatal AKI include a lack of decline in SCr within the first 7 days of birth, in addition to neonatal specific increases in SCr or cystatin C levels, or reduced urine output. (Table 12).

Table 12 | Criteria for AKI in neonates (any one or more of the following within the corresponding time period)

Neonatal AKI criteria
• No decline in SCr from birth to 7 days of life • Increase in SCr by ≥0.3 mg/dl (≥26.5 μmol/l) within 48 hours • Increase in SCr by ≥1.5 times baseline that is known or presumed to have occurred within the prior 7 days • Increase in serum cystatin C by 1.25 times baseline that is known or presumed to have occurred within the prior 7 days • Serum cystatin C >2.2 mg/dl • Urine output of less than 1.0 ml/kg/h for ≥24 hours

AKI, acute kidney injury; SCr, serum creatinine

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The definition of AKI in neonates requires modifications to the criteria for children and adults in order to ensure accurate identification. Neonatal GFR is low at birth due to immature kidney function, low kidney blood flow, and incomplete nephrogenesis, particularly in preterm neonates.[76-78] At birth, neonatal SCr primarily reflects maternal creatinine levels. Over the first approximately 7 postnatal days, neonates typically experience a physiologic decline in SCr, reflecting the transition from placental clearance to endogenous kidney function. A failure to decrease SCr during this time suggests the presence of AKI.[79, 80] The rate of this decline is gestational age-dependent, with more immature neonates demonstrating a slower decrease in SCr levels.[81, 82]

The 0.3 mg/dl increase within 48 hours and 1.5 times increase of SCr from baseline within 7 days criteria for neonatal AKI originate from the KDIGO 2012 AKI guideline.[12] Since then, numerous studies have demonstrated that these thresholds correlate with increased mortality and morbidity in neonates.[83-93] Notably, the neonatal KDIGO AKI definition uses the lowest prior SCr value as the baseline for comparison with subsequent SCr measurements.

Urine output plays a critical role in neonatal AKI identification and should be adapted to neonatal physiology. Technical challenges in neonatal urine output monitoring include the difficulty in obtaining accurate measurements due to the reliance on diaper weights, which can be imprecise due to mixing with stool and unmeasured voids. Indwelling catheters pose risks of infection and may not be feasible due to their small size. Neonates can experience transient oliguria followed by diuresis in the first few days of life before urine output stabilizes, making strict urine output thresholds difficult to apply. Given the dynamic nature of neonatal urine output, AKI definitions should incorporate adjusted urine output thresholds and require continuous 24-hour monitoring to account for fluctuations beyond the first 24 hours of life.

Investigators have explored refining AKI definitions based on chronological and gestational age, as AKI risk differs between extremely preterm neonates (<29 weeks gestational age) and more mature neonates.[94, 95] However, there is currently insufficient data to formally recommend gestational age-specific AKI definitions. Additionally, biomarkers such as urine NGAL and serum cystatin C offer potential improvements in early AKI detection. Urinary NGAL can serve as a noninvasive biomarker of tubular injury, though gestational age-specific reference values are still needed.[96, 97] Serum cystatin C has emerged as a promising biomarker for neonatal AKI, offering potential advantages over creatinine-based definitions. A large cohort study including over 50,000 neonates found that defining neonatal AKI as cystatin C ≥2.2 mg/l or an increase of ≥25% was 6.5 times more sensitive in predicting in-hospital mortality than SCr-based definitions.[98]

Training neonatal teams on AKI recognition can enhance early detection and intervention. While access to advanced biomarkers may be constrained in resource-limited

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settings, innovative and low-cost strategies, such as saliva-based blood urea nitrogen (BUN) testing, are being explored as noninvasive alternatives for estimating kidney function.[99] These approaches may provide pragmatic solutions for monitoring high-risk neonates when traditional serum testing is unavailable or impractical.

1.6.4. AKI staging in neonates

Practice Point 1.6.4.1: In neonates, the severity of AKI is staged according to individual components or combinations of the following SCr and urine output criteria (Table 13).

Table 13 | AKI staging criteria in neonates

Functional criteria			
Serum creatinine		**Urine output**	
Stage	**Criteria**	**Stage**	**Criteria**
C1	No decline in SCr from birth to 7 days of life, *Or* ≥0.3 mg/dl (26.5 µmol/l) increase, *Or* 1.5–1.9 times baseline	**U1**	>0.5 and ≤1.0 ml/kg/h for 24 h
C2	2–2.9 times baseline	**U2**	>0.3 and ≤0.5 ml/kg/h for 24 h
C3	≥3 times baseline *Or* Increase in SCr to ≥2.5 mg/dl (220 µmol/l), *Or* Initiation of RRT	**U3**	≤0.3 ml/kg/h for 24 h

C1-C3 indicates AKI severity stage according to serum creatinine (SCr) criteria, U1-U3 indicates AKI severity stage according to urine output criteria, B-/B+ indicates staging by absence or presence of an elevated damage biomarker. AKI, acute kidney injury; RRT, renal replacement therapy

Use of neonatal-specific thresholds for AKI staging enables more appropriate risk stratification for morbidity and mortality that can inform clinical management and follow-up. Large absolute changes in SCr are uncommon in neonates due to low muscle mass and physiologically low baseline GFR. The SCr criteria for Stage 3 AKI are reduced to 2.5 mg/dl in neonates, which represents a GFR of <10 ml/min per 1.73 m^2. However, it is important to recognize that even this reduced threshold may still be too high, particularly in preterm neonates with inherently lower baseline SCr values due to smaller muscle mass. In these populations, a SCr level of 2.5 mg/dl may reflect profound abnormal kidney function. Further study is warranted to refine this cutoff in preterm infants and better align AKI staging with meaningful clinical outcomes in this vulnerable group. In resource-rich settings, the inclusion of additional damage biomarkers such as NGAL and filtration markers such as serum cystatin C may enhance AKI severity staging.

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The use of neonatal-specific criteria introduces additional complexity and may be influenced by delayed creatinine kinetics or transient physiologic oliguria in neonates. There is a small risk of overestimating the severity of AKI using these criteria, particularly in preterm infants or those with non-kidney comorbidities that influence fluid status and creatinine handling. This may lead to a greater utilization of healthcare resources, including biomarker testing and nephrology consultations. These extra demands on resources are expected to be balanced by earlier recognition and timely treatment due to the high risk of morbidity and mortality associated with AKI severity in neonates. The potential for timely intervention and prevention of progression to kidney failure or death outweighs the risks of overdiagnosis and resource use in most clinical contexts.

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CHAPTER 2. AKI PREDICTION, RISK STRATIFICATION, AND DIAGNOSTIC EVALUATION

The risk of AKI is altered by the presence of factors that increase susceptibility to AKI in combination with exposures that cause AKI. There are several features that determine a person's susceptibility to AKI including demographic characteristics, genetics, social and environmental determinants, as well as comorbidities (acute or chronic conditions). Preexisting CKD and previous episodes of AKI represent major susceptibilities. Common exposures include conditions that alter fluid balance or hemodynamic status, infections, and nephrotoxic medications, which are more likely to lead to AKI in susceptible individuals. The interplay between susceptibilities and exposures is incompletely understood but it is generally recognized that a person's degree of susceptibility and intensity of exposures together increase their risk of developing AKI (Figure 4).

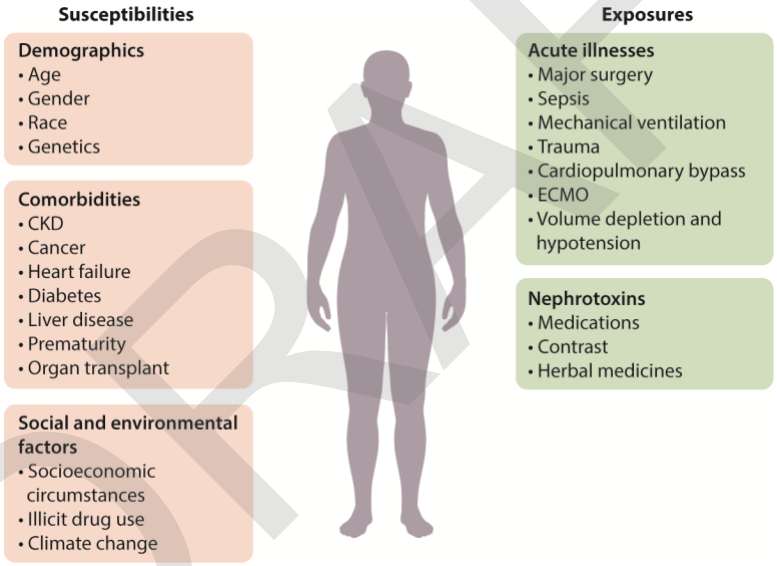

Figure 4 | AKI exposures and susceptibilities. AKI, acute kidney injury; CKD, chronic kidney disease; ECMO, extracorporeal membrane oxygenation

Recognition of a person's risk factors for developing AKI and associated adverse outcomes can be useful to target prevention and management strategies to people at risk. However, the risk of AKI changes in an individual person over time. Although it can be estimated at a given moment in time (e.g., at a preoperative clinic assessment or upon ICU admission), it is important to recognize that a person's risk is dynamic over the course of illness. Further, some exposures may be modifiable, and addressing these can reduce the risk of AKI. Susceptibilities and exposures for AKI can differ between community and hospital settings (Table 14). While there has been increasing knowledge of the epidemiology and outcomes of community-acquired AKI detected in hospital as well as community-acquired

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AKI detected in primary care, most current knowledge has been obtained from research on people in hospitals. Importantly, susceptibilities and exposures may interact in non-linear ways, such that the same exposure can confer markedly different AKI risk depending on baseline kidney function, frailty, comorbidity burden, and acute illness severity.

Table 14 | Common exposures and susceptibilities for community- and hospital-acquired AKI

Setting	Susceptibilities	Exposures
Community-acquired AKI	• Dehydration or poor access to water • Advanced age • Cognitive impairment • Low socioeconomic status • Preexisting CKD • Chronic heart disease • Chronic liver disease • Pregnancy • Limited access to healthcare • Underlying chronic infections (e.g., HIV, TB)	• Gastroenteritis (volume depletion) • Infections (e.g., pneumonia, leptospirosis, malaria, dengue) • Nephrotoxic herbal remedies and other complementary/alternative medicines • Snake bites and envenomation • Sepsis (community onset) • Obstructive uropathy (e.g., stones, prostate) • Uncontrolled diabetes or hypertension
Hospital-acquired AKI	• CKD • Prematurity • Diabetes • Heart disease, including congenital heart disease • Liver disease • Anemia • Advanced age • Malignancy • Polypharmacy • ICU stay	• Sepsis (hospital-acquired) • Major surgery (cardiac, abdominal, etc.) • Critical illness • Circulatory shock • Exposure to nephrotoxic medications • Radiocontrast agents • Mechanical ventilation • Solid organ or bone marrow transplant

AKI, acute kidney injury; CKD, chronic kidney disease; HIV, human immunodeficiency virus; ICU, intensive care unit; TB, tuberculosis

Figure 5 illustrates a risk stratification framework that integrates patient susceptibilities and clinical exposures, which can be achieved by integrating a variety of clinical tools to estimate a person's likelihood of developing AKI (or related outcome). This framework uses a tiered approach, beginning with identification of low-, moderate-, and high-risk people using tools such as clinical scoring systems, biomarkers, or predictive models that have been developed and validated in the specific clinical populations and settings where they are being applied. For people classified as low risk, regular standards of care may be appropriate whereas people at moderate or high risk may benefit from enhanced monitoring, additional risk assessment, or implementation of prevention or management strategies for AKI. The availability and feasibility of existing risk stratification tools varies across settings, and the choice of a particular tool will depend on local availability, cost, and expertise. Further, selection of an appropriate tool is context-specific and will vary by population and healthcare setting. A personalized approach that applies the right tool for the

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right patient, at the right time in their care is necessary to optimize early recognition of risk, appropriate interventions, and plan subsequent management, with the objective of reducing the incidence and/or severity of AKI and its associated adverse outcomes.

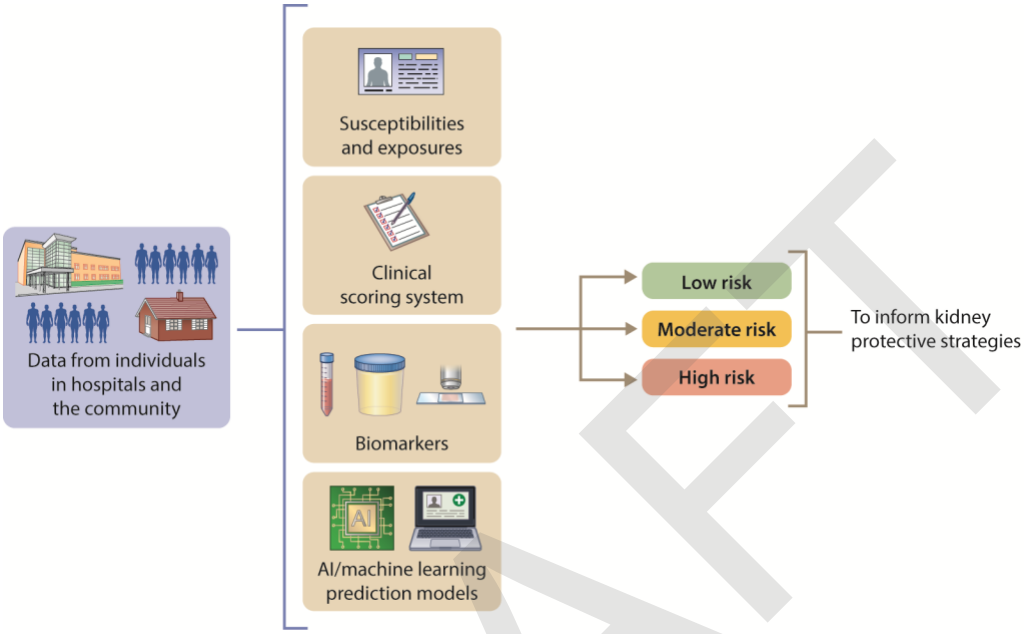

Figure 5 | Conceptual framework for AKI risk stratification. This figure illustrates a framework for classifying people by AKI risk across a continuum of clinical severity, integrating susceptibilities (e.g., age, comorbidities) and exposures (e.g., nephrotoxins, surgery, sepsis) (Figure 4) with clinical scoring systems, risk models, or biomarker data. Using these tools, people can be stratified into low, moderate, or high risk of AKI or related outcome to inform management. This approach supports proactive personalized AKI prevention, early recognition, and individualized management. AI, artificial intelligence

2.1. Risk prediction models

Recommendation 2.1.1: We suggest using externally validated clinical risk models to identify children and adults at increased risk of AKI and guide the use of kidney-protective strategies *(2C).*

This recommendation emphasizes the use of externally validated clinical risk models for early identification of children and adults at increased risk of AKI. Such models integrate multiple patient-level and contextual risk factors and have demonstrated significant discrimination and calibration for predicting AKI, supporting more consistent and objective risk stratification. Applying these tools in susceptible populations may enable more appropriate and efficient care through timely implementation of kidney-protective strategies to people at higher risk. This approach can also avoid unnecessary testing and intervention in people who are unlikely to benefit. Overall, this approach supports proactive, evidence-informed personalized care aimed at reducing AKI incidence and associated morbidity.

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Key information

Balance of benefits and harms

The primary benefit of using validated risk models is improved identification of children and adults at increased risk for AKI, enabling earlier and more targeted implementation of kidney-protective strategies in people at high risk, which may reduce AKI incidence, severity, and downstream complications. These models can standardize risk assessment, reduce reliance on subjective clinical judgment, and support more efficient use of preventive interventions in susceptible populations. Potential harms include overestimation of risk in some individuals, which could lead to unnecessary monitoring, interventions, or avoidance of beneficial therapies for underlying conditions. There is also a risk that poor integration of models into clinical systems can contribute to workflow burden. Embedding prediction models as electronic health record (EHR) alerts without linked action pathways may increase alert fatigue and reduce the effectiveness of decision support interventions. Overall, the anticipated benefits of more accurate risk stratification and targeted prevention are judged to outweigh the generally low and manageable potential harms when validated models are applied thoughtfully.

A systematic review and meta-analysis of 95 studies evaluating 302 externally validated AKI prediction models used in various populations at risk for AKI found substantial heterogeneity in model performance, though models generally demonstrated good discrimination upon external validation for prediction of AKI (overall pooled area under curve [AUC] 0.78, range 0.75–0.84 across hospitalization, ICU, post-contrast, and postoperative settings (Supplementary Table S16).[100] The cumulative evidence suggests most externally validated models perform well for predicting AKI onset, AKI severity, and post-AKI complications in hospitalized adults, supporting their use in care pathways to identify high-risk surgical and critically ill populations. These models enable early identification of people at elevated AKI risk but may also facilitate the targeted application of kidney-protective strategies. However, there is a high degree of inconsistency across studies regarding clinical settings, patient populations and predictive performance. Furthermore, models used different criteria for AKI. The predictive performance of models for the revised KDIGO AKI criteria is unknown.

Certainty of evidence

There is moderate certainty of evidence that the Mehta score, when used in adults undergoing cardiac surgery (the population of most studies), has low-to-moderate accuracy to predict AKI outcomes (specifically, low accuracy to predict incident AKI and moderate accuracy to predict Stage 3 AKI and RRT).[101-106] The level of accuracy was *a priori* defined as low for area under the curve (AUC) of 0.51–0.75 and moderate for AUC of 0.76–0.85. The certainty of evidence for predicting AKI was low, downgraded for methodological issues

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with the studies and inconsistency across the studies, but moderate for predicting stage 3 AKI and RRT, which were downgraded for methodological issues but had consistent findings across studies. Without evidence from trials analyzing clinical impacts, the overall certainty of evidence for implementing the Mehta score was downgraded, for indirectness, to low.

There is high certainty of evidence that the Simple Postoperative AKI risk (SPARK) score, when used in adults undergoing noncardiac surgery, has low accuracy (as defined in the prior paragraph) to predict AKI outcomes.[107-109] The certainty of evidence was high for prediction of incident AKI but moderate for Stage 3 AKI, downgraded for imprecision of the summary estimate. Without trial evidence, the overall certainty of evidence for implementing the SPARK score was downgraded, for indirectness, to moderate.

There is low certainty of evidence that prediction tools, in general, have (overall) moderate accuracy (as defined above) to predict AKI outcomes in both children and adults. This conclusion applies to prediction of incident AKI in various settings in children and adults and also other AKI-related outcomes and mortality in adults. The certainty of evidence was downgraded for methodological concerns of the studies, a high degree of inconsistency across studies, related to both statistical and clinical heterogeneity of studies conducted in different populations, settings, and with very different prediction models,[100] in addition to indirectness since the analyses do not provide evidence for any specific score. Since this analysis pertains to diagnostic accuracy and not the effect on clinical outcomes of implementing prediction tools, the overall certainty of evidence was downgraded, for indirectness, to very low for both children and adults.

Values and preferences

Identification of people at high risk of developing any form of AKI or progression to severe AKI or needing RRT is viewed positively by well-informed patients, in particular if the predictive models are based on routinely available data, do not require any additional investigations, are sufficiently accurate, and offer the prospect of potential preventive interventions to avoid AKI and subsequent adverse outcomes in vulnerable people.

Resource use and costs

Utilizing and applying most validated AKI risk models generally does not require significant additional direct costs for the patient or institution, as they primarily rely on healthcare professionals executing models using existing clinical data entered into an integer scoring system or computer-based calculator. The primary expense with systematic implementation of predictive models is the upfront and ongoing cost of integrating and updating (when necessary) the risk calculation within the existing information technology infrastructure of a hospital, such as an EHR. Further costs should be incurred to ensure the model continues to accurately calculate risk while other costs may arise from additional

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testing or treatments being applied to high-risk people. These potential harms may also be increased by the degree a model falsely classifies people as being at high risk for AKI, which could result in more unnecessary interventions and increased costs. However, overall, the primary economic argument for integrating AKI risk models into care is that they may lead to more targeted prevention efforts for AKI and related complications in people who are more likely to benefit, reducing the need for scarce or expensive downstream resources for care (e.g., ICU admission, RRT).[110]

Considerations for implementation

Successful implementation of AKI risk models requires initial investment and attention to specific clinical, technical, and institutional factors that impact model performance, uptake, and outcomes. Predictive risk models are only valuable if they are based on accurate and reliably collected predictor variables and delivered in a manner that supports clinical judgement. Implementation will achieve greater value when risk stratification is linked to specific, evidence-based interventions that can improve patient care and outcomes.

Rationale

Risk prediction models combine multiple patient-, procedure-, and/or care-related factors into a structured output on the probability of a future event for an individual person, which facilitates risk stratification and can guide the timely deployment of kidney-protective strategies in susceptible populations. Different risk models have been developed to predict AKI within specified time horizons and using variables ascertained as specific time points; for instance; for adults undergoing cardiac surgery (e.g., Mehta score; Supplementary Table S17) or major non-cardiac surgery (e.g., SPARK score; Supplementary Table S18), for people in the hospital, for people in the ICU,[100, 111, 112] and people with sepsis.[113, 114] In addition, risk prediction models have been developed and validated specifically for pediatric populations across different clinical settings, including hospitalized children,[115, 116] children in the pediatric intensive care unit (PICU),[117, 118] pediatric cardiac surgery patients,[119] and children with septic shock[120] (Recommendation 2.6.1; Supplementary Table S19). Model performance can vary depending on the specific patient population and features of the model. Significant heterogeneity in discrimination has been identified between externally validated models for AKI,[100] necessitating careful selection of models shown to have adequate performance and clinical utility in the population and clinical setting they will be used.

Most AKI risk models assess risk at a single time point, such as pre-surgery or upon ICU admission. Some newer models are dynamic, updating scores with data collected throughout the hospital stay. Examples include models adding intra- and postoperative data to improve the ability to predict postoperative AKI.[121, 122] Similarly, other studies have demonstrated that risk assessment improves with adding variables from day 1 or day 2 of a

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non-postoperative ICU stay.[111, 123] Thus, dynamic prediction of risk of AKI over time may provide insights into which patients warrant greater focus on preventive interventions over the course of an illness trajectory.

Recommendation 2.1.2: We recommend using externally validated clinical risk models to identify adults at risk of receiving renal replacement therapy (RRT) for AKI to inform patient choices and shared decision making about their care *(1C)*.

This recommendation places a high value on ensuring patients are provided with sufficient and accurate information on risks to inform their treatment decisions and that their values, preferences, and care choices are respected. The recommendations places a lower value on the harm, potential use of excess resources, and inconvenience that could result from clinically important overestimates of risk in a person who ultimately does not require support with RRT.

Key information

Balance of benefits and harms

Valid risk prediction models can help identify adults at higher risk of requiring RRT for AKI which can support timely, informed discussions about prognosis, treatment options, and care planning. These models can enhance shared decision-making by providing individualized risk estimates that help align clinical decisions with patient values and preferences. However, all existing prediction models were developed prior to landmark RRT timing trials.[124-128] A potential harm exists if the data supporting the model or data on the initiation of RRT changes and it increases the potential harm of incorrectly starting (or not starting) RRT (Chapter 5). Potential harms include misclassification of risk which may cause unnecessary anxiety, premature decision-making, or inappropriate preparation for RRT in some patients. Overreliance on model outputs could also diminish clinical judgment or lead to inequities if models are applied outside the populations in which they were validated. Overall, when used as adjuncts to clinical assessment, the benefits of improved prognostic clarity and patient-centered decision-making outweigh the relatively low risk of harm.

The Mehta score has been shown to predict need for RRT in adults undergoing cardiac surgery. Evidence review of data from 3 trials concluded that the predictive accuracy of the Mehta score was moderate with an AUC of 0.78 (0.69–0.87; Supplementary Table S17). There was no data on the accuracy of the SPARK score in adults undergoing major non-cardiac surgery.

Thakar *et al*. derived a clinical risk score in 33,217 participants undergoing cardiac surgery, reporting C-statistics of approximately 0.80 for postoperative AKI and 0.95 for dialysis-requiring AKI.[129] Similarly, Wijeysundera *et al*. developed and externally validated a simplified predictive index for RRT in a cohort of 928 participants, achieving AUCs of

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0.93–0.95.[130] Together, these large, diverse. inpatient cohorts, leveraging detailed perioperative and clinical variables, demonstrate that models built on real-world data can provide reasonably accurate estimates for predicting the need for RRT in AKI.

Zuo *et al*. validated a model for RRT requirement specifically for people with acute pancreatitis with excellent discrimination, calibration, and clinical utility, emphasizing that additional risk stratification for RRT for AKI can be achieved for disease-specific situations.[131] Models such as AKIpredictor[111] and those by Malhotra *et al*.[112] provide broader ICU applicability and can be incorporated into electronic systems to aid identification of people at high risk.

Certainty of evidence

There is moderate certainty of evidence that the Mehta score has moderate accuracy (defined as AUC between 0.76 and 0.85) to predict RRT in adults undergoing cardiac surgery (the population of most studies).[102-104] The certainty of evidence was downgraded for some methodological limitations of the studies. Without trial evidence, the overall certainty of evidence for implementing the Mehta score was downgraded, for indirectness, to low. Eligible studies conducted in children did not report RRT, nor did they evaluate the SPARK score to predict RRT specifically.

There is low certainty of evidence that prediction tools, in general, have (overall) moderate accuracy to predict RRT in adults. The certainty of evidence was downgraded for methodological concerns of the studies and a high degree of inconsistency across studies, related to both statistical and clinical heterogeneity of studies conducted in different populations, settings, and with very different prediction models,[100] in addition to indirectness since the analyses do not provide evidence for any specific score. Without trial evidence, the overall certainty of evidence for implementing the Mehta score was downgraded, for indirectness, to low. Eligible studies conducted in children did not report RRT.

Values and preferences

The initiation of RRT represents an escalation in medical care requirements, accompanied by increased utilization of healthcare resources, increased workload for healthcare professionals, prolonged hospitalization, and elevated healthcare expenditures. Receipt of RRT significantly impacts patient experience and burden of care, and most people want to avoid RRT, and if required, may benefit from being made aware and prepared to receive it. Identification of people at high risk of needing RRT is likely to be viewed positively by well-informed patients, in particular since it offers the prospect of potential preventive interventions, patient-centered counselling, earlier nephrology consultation, and timely preparation of RRT, including potential transfer to appropriate clinical settings such as ICU or a site with dialysis services.

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Resource use and costs

Use of validated risk models generally requires modest resources, as most models rely on routinely collected clinical and laboratory data already available in electronic health records. Implementation costs may include integration into clinical workflows or electronic systems, healthcare professional training, and periodic updates. These upfront investments are likely to be offset by more efficient use of resources through improved targeting of education, planning, and preparatory interventions for people at higher risk of RRT. As noted, a potential harm exists if the data supporting the model or evidence on the timing of RRT changes and the potential harm of incorrectly starting (or not starting) RRT increases (Chapter 5). Further, falsely classifying people as high risk for RRT can result from additional interventions and unnecessary transfer to an ICU or dialysis center. Earlier and better-informed shared decision-making may also reduce potentially avoidable or unwanted interventions and improve alignment of care with patient preferences. Overall, the resource requirements are considered reasonable relative to the potential benefits in care planning efficiency and patient-centered outcomes.

Considerations for implementation

Implementation of this recommendation requires selection of validated risk models for RRT that are appropriate for the local patient population and clinical setting. This is particularly important in rural and low-resource settings, as clinical practice patterns, access, and resources for RRT differ across jurisdictions necessitating steps to determine whether a model developed to predict RRT elsewhere (often a high-resource setting) provides accurate information in another setting.[129, 132-138] Integration of models into existing clinical workflows and EHRs is important to ensure timely access to risk estimates without adding undue burden to healthcare professionals. Healthcare professionals should receive training on model interpretation, limitations, and how to communicate risk clearly and sensitively to support shared decision-making. Risk models should be used as adjuncts to, rather than replacements for, clinical judgment and individualized patient assessment. Ongoing evaluation of model performance, equity, and patient understanding is important to ensure appropriate and effective use in practice.

Rationale

This recommendation is based on evidence that several externally validated risk models for AKI requiring RRT have shown very good calibration and discrimination,[129, 130, 138, 139] with overall pooled AUROC of 0.82 (95% CI: 0.79–0.85; Supplementary Tables S16), and with some individual external validation studies exhibiting AUROCs as high as 0.95. This has most consistently been demonstrated for models predicting postoperative RRT for AKI. Large inpatient cohorts have demonstrated that models based on routinely collected clinical and laboratory variables can perform well for preoperative prediction of the need for

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RRT for AKI following cardiac and major non-cardiac surgery.[122, 129, 140] Further, some research suggests these models can more accurately and consistently estimate a person's risk of progression to RRT than clinical judgment alone.[141] Reliable risk stratification supports timely, transparent discussions about prognosis, treatment options, and future care planning, which are central to shared decision-making. Providing patients with individualized, evidence-based risk information helps them to better understand potential trajectories and align decisions with their values and preferences. External validation increases confidence that these models can maintain performance in other populations and settings, although this should be tested in a new (external) population where a model for RRT that was derived elsewhere will be implemented. Overall, use of validated risk models promotes patient-centered, informed, and equitable decision-making around RRT for AKI.

Practice Point 2.1.1: In community and low-resource settings, simplified AKI risk scores can support early identification and management of adults at risk for community-acquired AKI.

In low resource, community-based settings, the ISN 0by25 multicenter feasibility study demonstrated that a simple symptom-based risk score (including vomiting, low oral intake, weakness, oliguria, hypotension, loss of appetite and swelling; Table 15) could be used to guide point-of-care (POC) SCr and urine dipstick testing, resulting in improved early AKI recognition and management. Across Bolivia, Nepal, and Malawi, 2101 people at moderate-to-high risk were identified using this score. After implementation of the POC driven protocol, more people with AKI were recognized (34.6% vs. 24.5%, $p<0.0001$).[142] This was associated with a reduction in hospital admissions from 59% to 49% ($p<0.001$).

Table 15 | International Society of Nephrology 0by25 study[a]–Clinical risk score for community-acquired acute kidney injury[142]

Risk factor	Points
History of kidney disease	1
Presence of oliguria	4
Infection with fever	1
Hypotension or shock	2
Pregnancy with hypertension/seizures	2
Whole body swelling	2
Loss of appetite	1
HIV on HAART	1
Coma/confusion	2
Anemia/pallor	1
Max total	**17**

[a]In the 0by25 feasibility study, among enrolled participants screened as moderate-to-high risk (score ≥3), the observed 7-day AKI risk was ~30% (severe AKI ~18%). Risk varied by kidney disease status at enrollment: No kidney disease 13.9% (98/705); acute kidney disease 36.6% (439/1199); and chronic kidney disease 46.2% (91/197). HIV, human immunodeficiency virus; HAART, highly active antiretroviral therapy

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These results support the practical application of simple risk tools in settings where conventional laboratory infrastructure is limited. By enabling frontline healthcare professionals to determine when to obtain SCr measurements, AKI was diagnosed and could be managed earlier.[142] Building on this model, the International Society of Nephrology (ISN) Kidney Care Network (KCN) applied this protocol across 4311 participants in Bolivia, Brazil, South Africa, and Nepal. AKI was substantially more common in those identified via the modified score (80.2%) than by clinical judgment alone (32.5%).[135, 143]

Together, these studies support clinical utility and scalability of simplified risk-based approaches for AKI screening in the community in low-resource settings. Incorporating such tools into primary healthcare workflows could enhance the timeliness and equity of AKI diagnosis, especially in under-served and high-risk communities.

Practice Point 2.1.2: The performance of electronic health record (EHR)-based AKI risk models should be tested in the settings they will be deployed. Harmonizing terminology and data structure within EHR systems and reassessment of performance over time is needed to ensure predictive accuracy in a local setting and over time.

Recent advances in machine learning and augmented intelligence (AI) using EHR data have expanded the development and testing of predictive models for AKI in acute care settings.[123, 132, 144-149] These techniques can identify key trends in variables collected from EHRs, such as routinely collected vital signs, lab results, nursing assessments, clinical conditions, and patient exposures, to predict the development of AKI. A systematic review and meta-analysis by Cama-Olivares *et al*. identified 95 machine learning models for AKI risk assessment, including models based on logistic regression, neural networks, random forests, and gradient boosting.[100] The pooled AUCs of these models for AKI prediction were 0.82 (95% CI: 0.80–0.84) upon internal validation and 0.78 (95% CI: 0.76–0.80) with external validation, highlighting the deterioration in model performance that can occur when models are applied in geographically and temporally distinct settings from their development. Many machine learning and AI risk models display excellent specificity and negative predictive value. However, these scores have often suffered from low positive predictive values (<50%) which has, in part, limited wide-scale implementation.[123, 132, 148] It is anticipated that more predictive models for AKI will arise in the future.

The performance of EHR-based AKI risk models depends on the quality, structure, and context of the data from which they are derived, making rigorous validation essential prior to clinical use. Local calibration is a critical component of implementation because data definitions, practice patterns, patient demographics, baseline AKI incidence, laboratory measurement practices, and thresholds for interventions can vary substantially across

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institutions, which may affect performance. Even previously externally validated models may systematically over- or under-estimate AKI risk if these setting-specific factors are not accounted for. Routine assessment of calibration-in-the-large and across risk strata enables institutions to update model outputs to ensure predictions remain trustworthy.

Effective implementation also requires harmonization of terminology, definitions, and data structures within EHR systems. Variability in coding practices, laboratory units, timestamps, and clinical concepts (e.g., AKI definitions or medication exposure) can impair model performance and limit their portability to new settings. Standardization using common data models and interoperable vocabularies facilitates consistent model execution and interpretation across sites.

Ongoing monitoring and periodic reassessment of model performance are necessary to maintain predictive accuracy over time. Changes in patient populations, clinical practices, data capture, and treatment strategies can lead to model drift, reducing reliability if left unaddressed. Continuous evaluation of discrimination (i.e., updating rankings of those with and without AKI) and calibration (i.e., aligning the predictions to the observed incidence and improving this over time), with timely updates when necessary are needed to ensure EHR-based AKI risk models retain accuracy in real-world clinical settings. Figure 6 illustrates a series of steps before and after implementation of an AKI risk model that can help ensure it operates more effectively.

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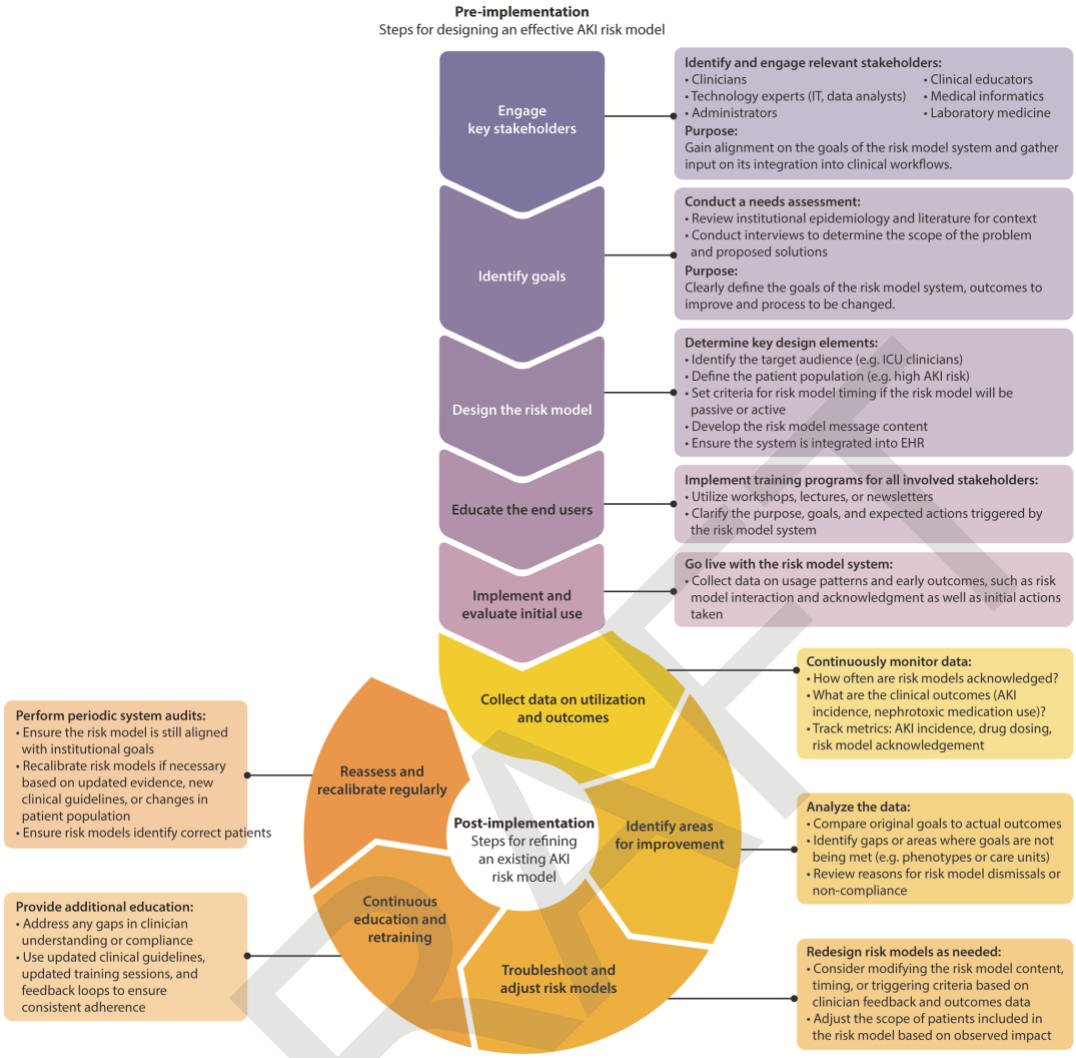
Pre-implementation
Steps for designing an effective AKI risk model
Engage key stakeholders
Identify and engage relevant stakeholders:
• Clinicians
• Technology experts (IT, data analysts)
• Administrators
• Clinical educators
• Medical informatics
• Laboratory medicine
Purpose:
Gain alignment on the goals of the risk model system and gather input on its integration into clinical workflows.
Identify goals
Conduct a needs assessment:
• Review institutional epidemiology and literature for context
• Conduct interviews to determine the scope of the problem and proposed solutions
Purpose:
Clearly define the goals of the risk model system, outcomes to improve and process to be changed.
Design the risk model
Determine key design elements:
• Identify the target audience (e.g. ICU clinicians)
• Define the patient population (e.g. high AKI risk)
• Set criteria for risk model timing if the risk model will be passive or active
• Develop the risk model message content
• Ensure the system is integrated into EHR
Educate the end users
Implement training programs for all involved stakeholders:
• Utilize workshops, lectures, or newsletters
• Clarify the purpose, goals, and expected actions triggered by the risk model system
Implement and evaluate initial use
Go live with the risk model system:
• Collect data on usage patterns and early outcomes, such as risk model interaction and acknowledgment as well as initial actions taken
Collect data on utilization and outcomes
Continuously monitor data:
• How often are risk models acknowledged?
• What are the clinical outcomes (AKI incidence, nephrotoxic medication use)?
• Track metrics: AKI incidence, drug dosing, risk model acknowledgement
Identify areas for improvement
Analyze the data:
• Compare original goals to actual outcomes
• Identify gaps or areas where goals are not being met (e.g. phenotypes or care units)
• Review reasons for risk model dismissals or non-compliance
Troubleshoot and adjust risk models
Redesign risk models as needed:
• Consider modifying the risk model content, timing, or triggering criteria based on clinician feedback and outcomes data
• Adjust the scope of patients included in the risk model based on observed impact
Continuous education and retraining
Provide additional education:
• Address any gaps in clinician understanding or compliance
• Use updated clinical guidelines, updated training sessions, and feedback loops to ensure consistent adherence
Reassess and recalibrate regularly
Perform periodic system audits:
• Ensure the risk model is still aligned with institutional goals
• Recalibrate risk models if necessary based on updated evidence, new clinical guidelines, or changes in patient population
• Ensure risk models identify correct patients
Post-implementation
Steps for refining an existing AKI risk model

Figure 6 | Pre- and post-implementation pathways for the development, validation, implementation, maintenance, and on-going evaluation of a clinical risk model (adapted from Quickfall et al 2024.[150] AKI, acute kidney injury; ICU, intensive care unit; IT, information technology

2.2. Electronic AKI alerts

Recommendation 2.2.1: We recommend against delivering interruptive, creatinine-based electronic alerts for AKI in isolation without systematic strategies for response in routine clinical care of adults (*1B*).

This recommendation applies to interruptive electronic alerts triggered by changes in SCr and implemented without an accompanying, structured response pathway. Electronic alert systems require significant effort and information technology infrastructure to develop and maintain. Evidence indicates that alerts may increase AKI recognition and have modest effects on clinical processes of care but alone do not consistently improve patient outcomes and may contribute to alert fatigue. If electronic AKI alerts are used, they should be

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embedded within a comprehensive care strategy that includes clear clinical guidance, accountability for response, and integration with multidisciplinary workflows aimed at timely evaluation and management of AKI.

Key information

Balance of benefits and harms

Electronic alerts to identify people with AKI can increase awareness of changes in kidney function and prompt earlier recognition of AKI. However, in clinical trials where SCr-based AKI alerts have been evaluated without standardized response protocols, clinical decision support, or accountability structures, they have not been shown to improve patient-centered outcomes such as mortality, need for RRT, or recovery of kidney function.

A meta-analysis of 13 randomized controlled trials (RCTs) comparing AKI alerts versus no alerts in a total of 29,979 adults at risk of AKI showed no significant differences in mortality (RR: 0.96; 95% CI: 0.91–1.02), progression to Stage 3 AKI (RR: 1.04; 95% CI: 0.79–1.36), need for RRT (RR: 1.02; 95% CI: 0.92–1.13), or development of MAKE (adjusted OR: 0.83; 95% CI: 0.67–1.03; Supplementary Table S20). There were also no differences in duration of AKI or chances of recovery of kidney function.

Potential harms of AKI include alert fatigue, workflow disruption, inappropriate or delayed clinical decision-making, overtesting, and therapeutic inertia due to overreliance on nonspecific SCr changes. Alerts based solely on SCr may also misclassify AKI, particularly in people with CKD, fluctuating volume status, or following introduction of medications that reduce GFR, leading to unnecessary interventions or consultations. Interruptive alerts can impose cognitive burden on healthcare professionals and may divert attention from higher-priority clinical tasks, especially in resource-constrained environments. At a system level, widespread implementation of isolated alerts consumes informatics and clinical resources without clear evidence of benefit and may erode healthcare professionals trust in electronic decision support tools.

Certainty of evidence

There is moderate certainty of evidence that, in adults, delivery of SCr-based electronic alerts for AKI identification alone, without systematic care strategies, do not improve AKI-related or other critical patient outcomes.[151-156] The certainty of evidence was downgraded for some methodological limitations.

Values and preferences

This recommendation reflects the value placed on patient-centered care and safety. Patients are likely to prioritize care models that lead to timely, coordinated, and effective responses to AKI risk over those that generate alerts without clear benefit, particularly when

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alerts may contribute to unnecessary testing, treatment, or delays in other aspects of care. Equity considerations were also important, as poorly designed alert systems may disproportionately burden settings with limited staffing or informatics support, potentially widening variation in care quality.

Healthcare professionals and healthcare systems generally place greater value on decision support tools that provide actionable information linked to recommendations that are integrated into care processes, rather than on early detection alone when such detection does not reliably translate into improved patient outcomes. Healthcare professionals and healthcare systems prefer to avoid alert fatigue, workflow disruption, cognitive overload, and false reassurance or inappropriate escalation, which may undermine electronic decision support systems.

Resource use and costs

Significant information technology resources are required to develop, implement, and maintain electronic AKI alerts. These systems may incur substantial costs related to informatics infrastructure, software development, validation, ongoing maintenance, healthcare professional training, and governance without corresponding reductions in AKI-related morbidity, mortality, or resource utilization.

In addition to direct implementation costs, interruptive alerts may generate indirect resource use through increased laboratory testing, consultations, documentation burden, and workflow inefficiencies triggered by nonactionable or low-specificity alerts. Alert fatigue may further diminish the efficiency of electronic clinical decision support systems (CDSS), potentially reducing the effectiveness of other high-value alerts and leading to downstream costs associated with missed or delayed responses to clinically important events.

Considerations for implementation

Implementation of this recommendation requires careful evaluation of existing EHR–based AKI detection tools and the clinical contexts in which they are deployed. Healthcare systems should assess whether current SCr-based alerts are linked to clearly defined response pathways, including standardized evaluation, management recommendations, escalation criteria, and accountability for follow-up. Where interruptive alerts are already in use without such supports, deimplementation or modification should be considered.

When electronic AKI detection is pursued, it should be embedded within a broader, systematic strategy for care. This may include integration with care bundles, clinical decision support tools, or consultative services, as well as clear delineation of roles and responsibilities among healthcare professionals. Local resources, staffing, and informatics capacity should be considered, as effective implementation requires ongoing monitoring of

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alert performance, healthcare professional engagement, and unintended consequences such as alert fatigue or inequitable burden across care settings. Education and training of healthcare professionals are important to ensure appropriate interpretation of AKI detection signals and alignment with recommended care processes in the settings they are delivered.

Rationale

The implementation of alerts is attractive because it theoretically provides a mechanism for increasing the rapidity of recognition and response to AKI. However, there is consistent evidence that electronic alerts for AKI based solely on SCr changes do not result in improvements in patient-centered outcomes in routine clinical care. While such alerts may increase recognition or documentation of AKI, detection alone does not ensure timely, appropriate, or effective clinical responses, particularly in the absence of standardized evaluation and management pathways.

Creatinine-based alerts are limited by delayed SCr kinetics, variable availability of baseline SCr measurements, and susceptibility to false-positive or clinically inconsequential triggers, which may reduce specificity and healthcare professional confidence. When delivered in an interruptive manner, these alerts may contribute to alert fatigue, workflow disruption, and desensitization to electronic decision support, potentially diminishing the impact of other high-priority alerts.

The Work Group judged that the balance of benefits and harms is unfavorable for isolated interruptive or non-interruptive alerts. Potential benefits related to earlier AKI identification are uncertain and inconsistent, whereas potential harms—including inefficient resource use, unnecessary testing or consultation, and erosion of healthcare professional trust—are well recognized.

This recommendation does not preclude the use of AKI alerts when embedded within multifaceted intervention strategies that include clear response pathways, education, and ongoing evaluation.

2.3. Kidney functional testing

Practice Point 2.3.1: Assessment of kidney functional reserve before a potential exposure may help to identify children and adults with an increased likelihood of developing AKI.

Kidney functional reserve is the kidney's capacity to increase GFR in response to physiological stress.[157] It has gained recognition as a measure for identifying people at increased risk of AKI, even when baseline GFR appears normal. Multiple methods exist to quantify kidney functional reserve, each with distinct advantages and limitations

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depending on the clinical setting (Table 16). Oral protein loading is a physiological, noninvasive approach suitable for stable outpatients or preoperative evaluation; however, its variability in protein content and delayed GFR response can limit reproducibility. Creatinine clearance, measured before and after protein loading, has traditionally been used to detect kidney functional reserve; however, its reliance on accurate urine collection limits its practicality.

In a study by Husain-Syed *et al*., adults undergoing elective cardiac surgery underwent preoperative kidney functional reserve assessment following a standardized oral protein load.[158] Although all participants had a normal resting GFR, those who developed postoperative AKI were characterized by significantly reduced kidney functional reserve. A kidney functional reserve ≤15 ml/min per 1.73 m² conferred an 11.8-fold increased risk of AKI, and the test had a high discrimination (AUC: 0.83) that was greater than observed for traditional kidney function markers.[158] In a prospective study of hematopoietic stem cell transplant recipients with normal pretransplant GFR, Mancianti *et al*. demonstrated that lower kidney functional reserve was associated not only with a higher risk of AKI but also with a reduced likelihood of kidney recovery.[159] A kidney functional reserve <20% was associated with a 5-fold increase in the risk of persistent abnormal kidney function. In children with prior kidney injury, such as those recovering from hemolytic uremic syndrome and posterior urethral valves, and children with congenital heart disease undergoing cardiac surgery with cardiopulmonary bypass, lower kidney functional reserve predicted long-term renal sequelae, including proteinuria.[160]

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Table 16 | Select clinical methods to measure kidney functional reserve

Method	Mechanism	Advantages	Limitations	Bedside application notes
Oral protein load (e.g., red meat, protein drink)	Stimulated GFR through dietary amino acids and humoral mediators	Noninvasive, physiologic	Variable protein content, slow onset (60–180 min), dietary restrictions	Can be used in stable patients; suitable preoperatively or in outpatient settings
Intravenous amino acid	Direct stimulation of GFR via systemic humoral effects	Rapid onset (30–60 min), controlled dosage	Requires intravenous access, not all amino acids are effective	Ideal for ICU/inpatient settings; more consistent dose
Creatinine clearance pre- and post-load	Compare GFR before and after protein load	Widely available, traditional method	Time-consuming (6+ hour), affected by tubular secretion	Requires close monitoring and timed urine collection
Cystatin C-based eGFR	Cystatin C changes post-protein load to reflect GFR shift	Less impacted by muscle mass, quicker than creatinine clearance	Not yet validated in clinical populations	Useful in ICU or elderly populations with low muscle mass
Inulin or iohexol clearance	Direct measurement of GFR with exogenous markers before and after protein load	Gold standard for GFR measurement	Invasive, expensive, less practical clinically	Mostly in research settings

AKI, acute kidney injury; (e)GFR, (estimated) glomerular filtration rate; ICU, intensive care

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Recommendation 2.3.1: We suggest using the furosemide stress test (FST) to assess the risk of progression to Stage 3 AKI, including RRT in adults (*2C*) and children (*2B*) with Stage 1 or 2 AKI who are euvolemic or hypervolemic.

This recommendation places a high value on identification of people with AKI who are at high risk of progressing to more severe AKI and could benefit from kidney-protective strategies and/or planning for RRT. It is based on evidence that the FST can provide a dynamic assessment of tubular function and help identify people who are at higher risk of progression to Stage 3 AKI, including the need for RRT. Use of the FST may support earlier risk stratification, closer monitoring, and timely escalation of kidney-protective or supportive strategies. The test should be performed using standardized dosing and urine output thresholds and interpreted in the context of overall clinical assessment.

Key information

Balance of benefits and harms

The primary benefit of applying the FST in people with early AKI is to improve risk stratification for progression to more severe AKI, including need for RRT by providing a functional assessment of tubular responsiveness. This information can support earlier identification of people at high risk, closer monitoring, timely nephrology consultation, patient counselling, and more proactive planning for supportive therapies such as RRT. The FST is relatively simple, inexpensive, and can be performed at the bedside using medications already familiar to healthcare professionals.[161]

Results from 12 studies show that the FST had low sensitivity and moderate specificity for prediction of Stage 3 AKI, and moderate sensitivity and low specificity for prediction of RRT in adults with critical illness or undergoing surgery (Supplementary Table S21). In critically ill children, the FST has also been shown to be predictive of RRT. However, different urine output cut-offs at 2 and 6 hours have been used (Supplementary Table S22).[162-165]

Multimodal approaches that combine the FST with clinical assessments or other biomarkers or risk scores have shown promise in identifying people at risk for AKI progression or need for RRT, but a standardized protocol for combination management in adults or pediatrics has yet to be widely validated.[166-168]

Potential harms include volume depletion, electrolyte abnormalities, or transient worsening of kidney function if the test is applied inappropriately to people who are hypovolemic or those without appropriate dosing and monitoring. In some cases, a poor urine output response may prompt unnecessary escalation of care or anxiety if results are overinterpreted outside the broader clinical context. There is also limited evidence on optimal

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thresholds in certain pediatric subgroups. Overall, when restricted to people who are euvolemic or hypervolemic and performed with standardized protocols and careful monitoring, the anticipated benefits of improved prognostic assessment outweigh the generally low and manageable risks.

Certainty of evidence

There is moderate certainty of evidence that, for adults who are critically ill or undergoing major surgery, the FST has low to moderate accuracy to predict AKI outcomes. The overall certainty of evidence was based primarily on the moderate certainty of evidence to predict RRT, which was downgraded for some inconsistency regarding specificity. There was low certainty of evidence for incident AKI, stage 3 AKI, and for the determination of low accuracy to predict death (low accuracy defined as 51%–75% sensitivity/specificity; moderate accuracy defined as 76%–89% sensitivity/specificity).[169-175] The certainty of evidence for these outcomes was downgraded for inconsistency and/or imprecision, and for possible publication bias regarding Stage 3 AKI. Without trial evidence, the overall certainty of evidence for implementing the FST was downgraded, for indirectness, to low in adults.

There is high certainty of evidence that, for children in the ICU or undergoing major surgery, the FST has low accuracy (as defined above) to predict incident AKI, Stage 3 AKI, and mortality, with possible high test accuracy to predict RRT.[162-165, 176-179] The evidence for mortality was inconsistent and imprecise and RRT was evaluated by only a single, imprecise study. Without trial evidence, the overall certainty of evidence for implementing the FST was downgraded, for indirectness, to moderate in children.

Values and preferences

Patients, caregivers, and healthcare professionals generally place a high value on early identification of worsening AKI, as progression to Stage 3. AKI is associated with increased complications, need for RRT, mortality, longer stay in hospital, and higher healthcare costs and resources. The FST aligns with these values by providing timely prognostic information that may help guide monitoring intensity, discussions about escalation of care, and anticipatory planning of care. Many well-informed patients and families are likely to prefer a bedside test using a familiar medication rather than waiting for clinical deterioration.

At the same time, some patients and healthcare professionals may place greater value on avoiding additional interventions, potential side effects of diuretics, or tests that do not directly alter treatment. Preferences may also vary in pediatric populations, where caregivers may be more cautious about medication exposure. Given this variability, the strength of the statement is Level 2, reflecting the importance of individualized discussion and shared decision-making. Overall, most patients and healthcare professionals are likely to favor use

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of the FST when the goal is improved prognostic clarity, provided it is applied judiciously and in appropriate clinical contexts.

Resource use and costs

The FST has minimal direct costs, as it uses an inexpensive, widely available medication and relies on routine bedside monitoring of urine output. It does not require specialized equipment, advanced imaging, or additional laboratory testing beyond standard AKI care, making it feasible in a wide range of clinical settings, including resource-limited environments. Some additional nursing time may be required to administer the dose and closely monitor urine output over the testing period.

Use of the FST may lead to downstream resource implications by prompting closer monitoring, earlier nephrology consultation, or escalation of care in people identified as high risk, which could increase short-term resource utilization. However, improved risk stratification may also enable more efficient allocation of resources by focusing intensive monitoring and interventions on people most likely to progress. Overall, the low cost and simplicity of the FST, combined with its potential to support more targeted use of healthcare resources, suggest a favourable balance between costs and anticipated clinical value.

Considerations for implementation

The FST consists of a protocolized (1 mg/kg or 1.5 mg/kg) dose of intravenous furosemide administered to people with Stage 1 or 2 euvolemic or hypervolemic AKI to assess the risk of progression to more severe AKI (Figure 7).[169] Results from prospective observational studies and RCTs have demonstrated that adults who make a limited volume of urine (e.g., <200 ml in the 2 hours after the receipt of intravenous furosemide) are more likely to experience AKI progression to Stage 3 AKI (including the need for RRT) in the next 14 days.[161, 171, 180, 181]

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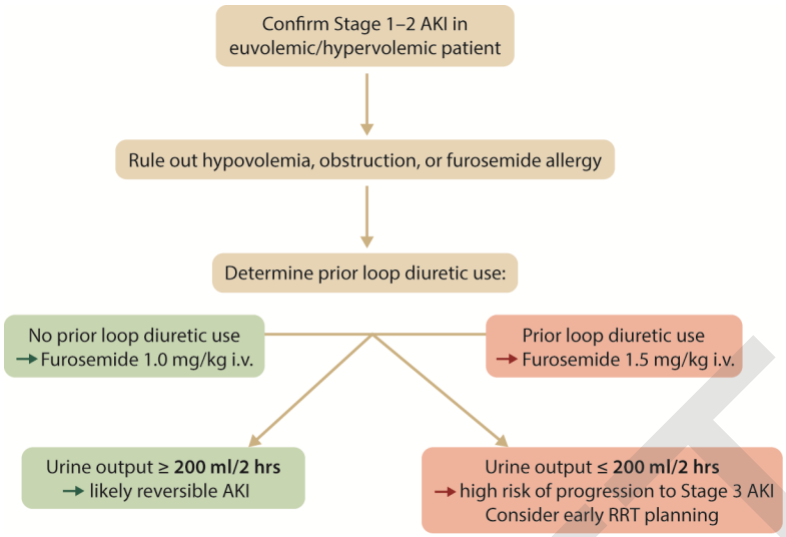
Confirm Stage 1–2 AKI in euvolemic/hypervolemic patient
Rule out hypovolemia, obstruction, or furosemide allergy
Determine prior loop diuretic use:
No prior loop diuretic use
→ Furosemide 1.0 mg/kg i.v.
Prior loop diuretic use
→ Furosemide 1.5 mg/kg i.v.
Urine output ≥ 200 ml/2 hrs
→ likely reversible AKI
Urine output ≤ 200 ml/2 hrs
→ high risk of progression to Stage 3 AKI
Consider early RRT planning

7 | Application of the furosemide stress test in the setting of early mild-to-moderate AKI in adults. In critically ill children, the furosemide stress test typically uses a urine output criterion of <2 ml/kg/hour over 2 hours. AKI, acute kidney injury; i.v., intravenous; RRT, renal replacement therapy

Implementation of the FST requires careful patient selection to ensure it is used only in children and adults with Stage 1 or 2 AKI who are euvolemic or hypervolemic, as use in people who are hypovolemic may increase the risk of harm. Standardized protocols for dosing, timing, and urine output measurement should be established to promote consistent application and interpretation across care teams. Healthcare professionals, including nursing staff, should be trained on the purpose of the test, appropriate monitoring, and recognition of adverse effects, such as hypotension or electrolyte disturbances.

Interpretation of the FST should consider recent loop diuretic exposure. In people already receiving high-dose loop diuretics or with suspected diuretic resistance, the incremental diagnostic/prognostic value of the FST may be attenuated, and a lack of response should be interpreted cautiously.

The results of the FST should be interpreted in the context of the overall clinical picture and used as an adjunctive prognostic tool rather than a standalone determinant of management decisions. Clear guidance is needed on how test results will inform downstream actions. For example, non-response could trigger a prespecified bundle, including closer urine output/serum creatinine monitoring, medication review for potential nephrotoxins, hemodynamic reassessment, and (where appropriate) early preparation for RRT. Consideration should also be given to pediatric-specific dosing, thresholds, and caregiver communication. Ongoing evaluation of test use, safety, and impact on clinical decision making can ensure appropriate and effective implementation in practice.

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Rationale

Use of the FST to refine risk stratification of people at high or low risk for severe AKI and RRT can facilitate clinical decision making, support counselling, facilitate planning of scarce resources and enable timely preparation for RRT before the development of complications, The test is feasible to use in appropriately selected people across diverse clinical settings worldwide.

Recommendation 2.3.2: We suggest calculating kinetic estimated glomerular filtration rate (KeGFR) in hospitalized adults with or at risk of AKI when an estimate of GFR under non-steady-state conditions will affect clinical decision-making *(2B)*.

This recommendation acknowledges that traditional eGFR equations assume steady-state kidney function and will provide misleading estimates of GFR in the setting of rapidly changing SCr concentration. Kinetic estimated glomerular filtration rate (KeGFR) incorporates the rate of change in SCr, providing a more physiologically appropriate estimate of GFR during acute illness. When clinical decisions such as medication dosing, nephrotoxic exposure, or escalation of care depend on an estimate of GFR, KeGFR may offer additional, clinically relevant information to aid decision-making. Its use should be targeted to situations in which nonsteady-state conditions are present and results are likely to influence management.

Key information

Balance of benefits and harms

The kinetic KeGFR is designed to estimate kidney function under non-steady-state conditions by evaluating serial SCr measurements. Unlike traditional eGFR equations, which assume steady-state kinetics, KeGFR accounts for rapid fluctuations in SCr that occur in evolving AKI. Several equations, most notably the Chen formula, have been developed to interpret SCr kinetics in dynamic settings.[182]

The main benefit of calculating KeGFR is improved estimation of kidney function during nonsteady-state conditions, when SCr is changing and conventional eGFR equations (that assume steady-state SCr) may be inaccurate. More accurate assessment of real-time GFR can support safer and more appropriate clinical decisions, such as medication dosing, avoidance of nephrotoxins, or use of contrast, potentially reducing preventable harm. KeGFR may also enhance healthcare professional understanding of the trajectory and severity of AKI, which can inform care planning.

KeGFR has moderate accuracy (defined as AUC of 0.76–0.85) to predict incident AKI and may have high accuracy to predict the need for RRT in adult surgical or medical patients at high risk of AKI (Supplementary Table S23).[183-185] In critically ill adults with

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sepsis, KeGFR combined with urine output criteria has been found to have high sensitivity (defined as ≥90%) with low specificity (defined as 51%–75%) to predict incident AKI and moderate accuracy to predict the need for RRT (Supplementary Table S24).[186] Importantly, studies have shown that KeGFR was more accurate at predicting AKI and need for RRT than traditional eGFR equations that assume steady state of SCr.[185, 187]

Potential harms are limited but include misinterpretation of results, particularly if healthcare professionals are unfamiliar with the assumptions and limitations of KeGFR calculations. Overreliance on KeGFR in isolation could lead to inappropriate decisions if other clinical factors are not considered. There is also some uncertainty related to variability in calculation methods and requirements for more than one, timed SCr measurement for the calculation. Overall, when used selectively and interpreted within the broader clinical context, the anticipated benefits of improved KeGFR estimation outweigh the low risk of harm.

Certainty of evidence

There is high certainty of evidence that KeGFR has moderate accuracy (defined as AUC of 0.76–0.85) to predict incident AKI in adults with medical or surgical risks for AKI.[185, 188, 189] The certainty of evidence to predict RRT, however, was low, downgraded for sparseness. Without trial evidence, the overall certainty of evidence for implementing KeGFR was downgraded, for indirectness, to moderate in adults.

There is low certainty of evidence that assigning adults to their worst prediction category according to either KeGFR or KDIGO urine output criteria has high sensitivity (defined as ≥90%), but low specificity (defined as 51%–75%), to predict incident AKI, moderate accuracy (defined as AUC 0.76–0.85) to predict RRT, and low accuracy (defined as AUC 0.51–0.75) to predict mortality.[186] The certainty of evidence was downgraded for being based on a single, large study that did not provide confidence intervals (estimates of precision). Without trial evidence, the overall certainty of evidence for implementing KeGFR or KDIGO urine output criteria categorization was downgraded, for indirectness, to very low in adults.

Values and preferences

Well-informed patients and healthcare professionals generally place high value on accurate assessment of kidney function when decisions carry meaningful risks. KeGFR aligns with this value by providing a more appropriate estimate of GFR during acute changes in kidney function, when traditional eGFR may be misleading. Healthcare professionals value tools that can improve decision-making precision, particularly in people in the hospital at complex or high-risk.

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Preferences may vary due to unfamiliarity with KeGFR, concerns about the validity of the calculation, or uncertainty about how to incorporate the estimate into routine care. Some healthcare professionals may value simplicity and consistency with established eGFR measures, and changes in SCr, especially when kinetic estimates are unlikely to change management. For patients and caregivers, the value lies primarily in safer and more individualized care rather than the specific calculation used. Overall, this Level 2 statement reflects variability in preferences and emphasizes selective use when KeGFR is most likely to inform clinical decisions.

Resource use and costs

Calculating KeGFR has minimal direct costs, as it uses routinely collected SCr results and patient characteristics already available in people in the hospital. Resource use may include modest healthcare professional time for calculation or review and potential information technology suppose if KeGFR is integrated into EHR systems. Targeted use of KeGFR may lead to downstream cost implications by influencing medication dosing, contrast use, or monitoring intensity, but these effects are primarily aimed at improving safety rather than increasing utilization. Overall, the resource requirements are low, and the potential for improved clinical decision-making suggests a favorable balance between costs and anticipated benefit when used selectively.

Considerations for implementation

Implementation of KeGFR requires clear identification of clinical scenarios in which non–steady state kidney function is present and the estimate is likely to influence management. Several equations exist.[190] The Chen formula is written as:

$$KeGFR = eGFR_{SS} \times SCr_{SS}/SCr_{Mean} \times (1 - 24 \times [\Delta SCr/\Delta Time\ (hr)]/[\Delta SCr_{Max}/\Delta Time_{Max}]),$$

where SS indicates values at steady state (prior to AKI episode), SCr_{Mean} is the average of the 2 measurements of SCr being evaluated, $\Delta SCr/\Delta Time$ is the change in SCr divided by the period of time, in hours, between SCr measurements, and $\Delta SCr_{Max}/\Delta Time_{Max}$ is the maximum theoretic change possible in SCr per day.[190] Other formulas are available online.

Healthcare systems should agree on a standardized KeGFR formula and assumptions, as multiple methods exist and inconsistent use may lead to confusion or misinterpretation.[190] Integration into EHR systems, with automated calculation using routinely available SCr data, can reduce healthcare professional burden and improve reliability. The increasing availability of POC SCr testing can facilitate clinical application in remote or low-resource settings. Education and training are important to ensure healthcare professionals understand how KeGFR differs from conventional eGFR, including its strengths, limitations, and appropriate

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interpretation. Results should be presented as an adjunct to clinical judgment rather than a standalone decision tool.

Rationale

KeGFR has diagnostic and prognostic utility in children and adults under non–steady-state conditions when SCr is changing and conventional eGFR estimates are unreliable. Estimating KeGFR may support clinical decision-making because an estimate of kidney function during rapidly changing SCr can inform time-sensitive decisions such as drug dosing, continuation or avoidance of potentially nephrotoxic medications, and the intensity of monitoring or level of care. However, KeGFR estimates have important limitations and may be less reliable when creatinine generation is changing (e.g., critical illness, malnutrition), when volume status and fluid balance are fluctuating (dilution/concentration effects), or when serum creatinine measurements are infrequent or delayed.

2.4. Biomarkers for AKI risk stratification

Practice Point 2.4.1: Baseline albuminuria (measured by urine albumin-to-creatinine ratio [UACR or dipstick protein testing]) offers additional prognostic value to eGFR for evaluating AKI risk in adults across various settings.

Measurement of baseline albuminuria, in addition to eGFR, provides valuable prognostic information for identifying people at higher risk for AKI. Large observational studies, including the Atherosclerosis Risk in Communities (ARIC) cohort[191], the Alberta Kidney Disease Network[192], and the Assessment, Serial Evaluation, and Subsequent Sequelae in Acute Kidney Injury (ASSESS-AKI) study[193], have consistently demonstrated that elevated UACR and proteinuria by dipstick are independently associated with greater risks of AKI and AKI requiring dialysis, even after accounting for baseline eGFR and comorbidities. For example, in the ARIC cohort, including over 11,000 participants, the risk of AKI rose progressively with increasing albuminuria and decreasing eGFR, with consistent effects across age, sex, and race (Table 17).[191]

A meta-analysis of studies, including 1.28 million participants with baseline measures of albuminuria and eGFR, confirmed these findings and highlighted that greater albuminuria as well as lower eGFR both significantly elevated the risk of AKI, independent of diabetes and hypertension (Figure 8).[194] In an individual participant data meta-analysis of 49 cohorts, lower eGFR and more severe albuminuria were each associated with higher rates of AKI.

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Acute kidney injury: 49 cohorts
23 914 614 participants; 1 408 929 events

	Urine albumin-creatinine ratio, mg/g				
eGFRcr	<10	10–29	30–299	300–999	1000+
105+	1.0	1.6	2.4	3.7	5.5
90–104	ref	1.4	2.1	3.2	5.0
60–89	1.6	2.2	3.1	4.3	6.7
45–59	3.5	4.0	5.1	6.9	9.0
30–44	5.6	5.9	6.8	8.6	11
15–29	8.3	8.0	8.5	9.9	10
<15	8.5	11	7.9	5.5	5.7

Figure 8 | Associations of CKD staging by eGFRcr and UACR categories and risks for AKI in multivariable-adjusted analyses. Numbers reflect the adjusted hazard ratio compared with the reference cell. Adjustment variables included age, sex, smoking status (current, former, or never), systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, body mass index, use of antihypertensive medications, and a medical history of diabetes, coronary heart disease, stroke, heart failure, atrial fibrillation, peripheral artery disease, cancer, and chronic obstructive pulmonary disease, where relevant. The colors were determined for each outcome separately using the following rule: the percentile shaded the darkest green color corresponds to the proportion of cells in the grid without CKD (e.g., 6 of 35 cells with eGFR ≥60 ml/ min per 1.73 m^2 and ACR. AKI, acute kidney injury; CKD, chronic kidney disease; eGFRcr, estimated glomerular filtration rate by creatinine; UACR, urine albumin-to-creatinine ratio

The association of albuminuria with AKI has been consistently identified in numerous clinical settings and populations (Table 17). In people with stroke, proteinuria was associated with a 5-fold increase in the risk of contrast-associated AKI.[195] In the ICU setting, albuminuria identified within 24 hours of admission predicted progression to severe AKI.[196] Preoperative albuminuria independently predicted AKI after cardiac and noncardiac surgery,[139, 197] while postoperative albuminuria also predicted subsequent AKI.[198] Among veterans undergoing coronary artery bypass graft (CABG) surgery, higher preoperative UACR was associated with an increased risk of AKI, a longer hospital stay, and higher mortality.[199] In people with CKD G3–G4 undergoing surgery, even mild dipstick proteinuria increased the risk of AKI and RRT.[200] A dose-dependent relationship, with increased AKI risk emerging with even trace dipstick proteinuria has also been demonstrated in non-cardiac surgery.[201] The NARA-AKI study reinforced these findings in adults undergoing non-cardiac surgery, showing a graded AKI risk based on dipstick proteinuria levels.[202] Albuminuria measurement is low-cost, non-invasive, and globally accessible, supporting its use as a feasible, practical addition to risk stratification frameworks for AKI.

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Table 17 | Select studies identifying albuminuria as a risk factor for AKI

Study author, year	Population	Measurement type and timing	Outcome	Key findings
Hsu, 2008[203]	1746 hospitalized adults	Preexisting dipstick proteinuria	Dialysis-requiring AKI	Preexisting proteinuria associated with high AKI risk
Grams, 2010[191]	11,200 (ARIC cohort)	UACR (subclinical to severely increased albuminuria)	AKI	Graded association of UACR with AKI, independent of eGFR
James, 2010[192]	~920,000 community adults (Canada)	Dipstick proteinuria and UACR	AKI	Graded AKI risk with increasing proteinuria, independent of eGFR
Huang, 2011[204]	1052 participants undergoing cardiac surgery	Preoperative dipstick proteinuria	AKI	Proteinuria independently predicted AKI after surgery
Molnar, 2012[198]	1198 participants undergoing cardiac surgery	Postoperative albuminuria	Postoperative AKI	Postoperative albuminuria predicted AKI before SCr rise
Zappitelli, 2012[198]	294 children undergoing cardiac surgery	Preoperative UACR	Postoperative AKI	No association found in pediatric population
Wahl, 2018[201]	153,767 participants undergoing noncardiac surgery	Preoperative dipstick proteinuria	Postoperative AKI	Dose-dependent AKI risk with proteinuria, independent of eGFR
Lee, 2018[205]	5347 adults with dialysis-requiring AKI	Preadmission proteinuria	Non-resolution after AKI	Proteinuria associated with reduced resolution post-AKI
Parr, 2018[206]	90,614 AKI survivors vs. controls	Dipstick proteinuria	New/progressive proteinuria post-AKI	Higher odds of worsening proteinuria post-AKI
George 2015[199]	5968 VA patients undergoing CABG	Preoperative UACR ≥30 mg/g	Postoperative AKI, mortality	Higher UACR linked to increased risk of AKI, hospital stay, mortality
James, 2015[194]	Meta-analysis of 1.28 million participants	UACR	AKI	Higher UACR associated with increased AKI risk

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Neyra, 2014[196]	Participants in the ICU with sepsis	*De novo* albuminuria	Severe AKI	*De novo* albuminuria associated with severe AKI progression
Tao, 2017[195]	2015 participants who have had a stroke	Dipstick proteinuria/ UACR >30 mg/g	CA-AKI, 1-year mortality	5x risk of CA-AKI; higher mortality with proteinuria
Hsu, 2020[207]	1538 participants post-AKI	UACR post-AKI (3 months)	CKD progression	Post-AKI albuminuria linked to faster CKD progression
Nishimoto, 2020[202]	5168 participants undergoing noncardiac surgery	Preoperative dipstick proteinuria	Postoperative AKI	Graded AKI risk by dipstick level; independent of comorbidities
Jiang, 2023[208]	1546 participants with CKD G3–G4 (cardiac surgery)	Dipstick (trace to 3+)	Postoperative AKI, AKI-RRT	Proteinuria predicted AKI and RRT; risk increased with severity

AKI, acute kidney injury; ARIC, Atherosclerosis Risk in Communities; CABG, coronary artery bypass graft; CKD, chronic kidney disease; CA-AKI, contrast-induced AKI; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; RRT, renal replacement therapy; SCr, serum creatinine; UACR, urinary albumin-to-creatinine ratio; VA, Veterans Affairs

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Recommendation 2.4.1: In acute care settings where children and adults are susceptible to AKI, we suggest using biomarkers of kidney tubular stress or damage according to their clinically validated and regulatory approved indication for the early identification of people at risk of moderate or severe AKI, to inform targeted kidney-protective strategies (*adults: 2B; children: 2C)*.

Practice Point 2.4.2: Biomarkers of kidney stress (e.g., urine [TIMP-2]*[IGFBP7]) can be used to assess the risk of moderate-to-severe AKI in critically ill adults, especially within the first 12 hours of ICU admission or after high-risk events including major surgery or sepsis.

Practice Point 2.4.3: Biomarkers of kidney damage (e.g., urine NGAL) can be used to identify children and adults at high risk of severe AKI in hospital settings.

Measurement of kidney stress and damage biomarkers in susceptible children and adults can identify critically ill people at high risk for severe AKI who may benefit from early application of targeted kidney-protective strategies. This recommendation and related practice points (2.4.2. and 2.4.3) place a high value on delivering preventive strategies to high-risk people to reduce the risk of progression to severe AKI and its complications. The recommendation acknowledges that additional resource use (time and costs) is required to implement these tests, and that a strategy of targeting preventive interventions to high-risk people can be more efficient or appropriate than applying this care to all patients. To maximize the value of additional biomarker testing, this should be done in conjunction with a systematic strategy for providing kidney-protective interventions to patients identified at increased risk in acute care settings.

Key information

Balance of benefits and harms

The benefits of using validated biomarkers of kidney stress or damage arise from the earlier identification of people at high risk of developing severe AKI, often before changes in SCr or urine output are evident. Early risk recognition can support timely implementation of targeted kidney-protective strategies, which may reduce AKI severity and associated complications. Biomarkers may improve risk stratification beyond traditional clinical measures. Large prospective cohort studies show that selected biomarkers of kidney stress or damage can identify people at increased risk of developing severe AKI 12–24 hours earlier than traditional markers such as SCr or urine output.[32, 197, 209-212]

[TIMP-2][IGFBP7]:* Urinary concentrations of TIMP-2 and IGFBP7 have been shown to increase in response to renal tubular stress from multiple causes including ischemia, inflammation, drugs, and toxins before SCr rises or urine output decreases among people who develop AKI.[213-216] The value of urinary [TIMP-2]*[IGFBP7] to predict early postoperative moderate-to-severe AKI has been demonstrated in numerous prospective,

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observational studies of patients with critical illness, following major surgery, with septic shock, and severe heart failure. RCTs have used measurement of this biomarker early after surgery to identify high risk participants to target with AKI preventive interventions.

RCTs that tested the effectiveness of kidney-protective strategies among adults with elevated urinary [TIMP-2]*[IGFBP7] concentrations suggest that measurement of [TIMP-2]*[IGFBP7] can be a valuable tool to identify people who can benefit from postoperative application of kidney protection strategies (Supplementary Table S26). In the Prevention of AKI (PrevAKI) trial, 276 adults with a urinary [TIMP-2]*[IGFBP7] ≥0.3 in the early postoperative period following cardiac surgery were randomized to receive a kidney-protective strategy based on recommendations from the KDIGO 2012 AKI Guideline versus usual care.[4] The study showed a reduced risk of any stage of AKI from 72% in the usual care arm to 55% in the intervention arm (p=0.004). More specifically there was less Stage 2 and 3 AKI in those receiving the intervention (30%) than in the usual care arm (45%), p=0.009.[4]

The BigpAK RCT similarly evaluated a biomarker-based intervention to prevent AKI after major surgery among critically ill participants who had undergone major abdominal surgery.[5] This trial identified participants with urinary [TIMP-2]*[IGFBP7] ≥0.3, who were randomized to receive an intervention based on the KDIGO 2012 AKI Guideline kidney-protective strategies or usual care. While there was no difference in overall AKI incidence (any stage) or inpatient mortality, the study did demonstrate a reduction in Stage 2 and 3AKI, shorter length of ICU stay, and a reduction in the cost of care for those randomized to the intervention strategy.[5] The BigpAK-2 trial repeated this approach in a larger, international, validation RCT in 1180 high risk adults undergoing major surgery with elevated urinary [TIMP-2]*[IGFBP7] ≥0.3. Application of a kidney-protective strategy consisting of supportive measures and avoidance of nephrotoxins resulted in a significantly lower risk of moderate-to-severe (Stage 2 or 3) AKI compared to standard care (22.3% vs. 14.4%), without increasing adverse events.[6, 217]

Evidence review of 19 studies showed that urinary [TIMP-2]*[IGFBP7] ≥0.3 had high sensitivity (90%) but poor specificity (53%) for predicting moderate or severe (Stage 2 or 3) AKI in adults,[218] but lower sensitivity (68%) to predict any incident AKI (Supplementary Table S27). At a higher cut-off of ≥2.0, sensitivity was poor (33%) but specificity was high (95%) for predicting moderate to severe AKI in adults. Evidence review of 5 pediatric studies found that urinary [TIMP-2]*[IGFBP7] had moderate accuracy (AUC 0.79) to predict moderate or severe AKI in children (Supplementary Table S28).[16]

There are several biomarkers of tubular damage that can be detected in urine and plasma prior to changes in SCr and urine output, which have been associated with an increased risk of impending AKI; however few have received regulatory approval for entry into clinical use (Table 4).

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NGAL: The 25-kDa monomer of NGAL is produced by renal tubular epithelial cells, and increased concentrations in urine or plasma serve as indicators of renal tubular injury.[219] Urine NGAL is more specific for detection and evaluation of AKI than plasma NGAL and has been U.S. Food and Drug Administration (FDA) cleared as an adjunctive risk assessment tool for moderate-to-severe AKI in children who are critically ill in the ICU.[220] In Europe, it is European Conformity (CE)-marked for early detection and evaluation of AKI in hospital settings.

Urine NGAL has been shown to predict progression to Stage 2 or 3 AKI and need for RRT in children and adults. Urine NGAL can be combined with other markers of GFR to identify those at highest risk for the most severe forms of AKI. For example, Goldstein *et al*. demonstrated that the combination of urine NGAL and plasma cystatin C collected after the start of cardiopulmonary bypass provided a more accurate prediction of severe (Stage 2 or 3) AKI within 7 days compared to a rise in SCr of ≥50%.[221]

Evidence review of 35 studies with 8374 participants showed that urine NGAL has moderate sensitivity (77%) and specificity (81%) to predict incident AKI in adults (Supplementary Table S29).[218] Six of these studies reported that urine NGAL had low sensitivity (68%) and moderate specificity (83%) to predict Stage 2 or 3 AKI (sensitivity 68%, specificity 83%) and need for RRT (sensitivity 65%, specificity 89%) in adults. Across 28 pediatric studies with 3459 participants, urine NGAL had moderate accuracy to predict AKI (sensitivity 75%, specificity 85%), severe AKI (AUC 0.80), need for RRT (AUC 0.78), as well as high accuracy for prediction of mortality (AUC 0.87) in children (Supplementary Table S30).[16]

KIM-1: This glycoprotein is produced by proximal tubular cell and is released into urine after tubular cell damage. Urine KIM-1 received U.S. FDA approval as a biomarker only for use in a research context, specifically as part of a panel of nephrotoxicity biomarkers for use in preclinical drug development. The evidence review found that, in adults, urine KIM-1 had moderate sensitivity (76%) and specificity (79%) for early detection of AKI (14 studies[218] of 2993 participants; Supplementary Table S31)) and, in children, low accuracy (AUC 0.70) to predict AKI (12 studies with 1593 participants[16]) and Stage 2 to 3 AKI (AUC 0.73), but moderate accuracy, from a single RCT, to predict need for RRT (AUC 0.76) and death (AUC 0.78; Supplementary Table S32).

L-FABP: This biomarker is excreted into urine after tubular cell damage. The evidence review found that L-FABP had low sensitivity (70%) and moderate specificity (81%) to predict AKI in adults (sensitivity 10 studies;[218] Supplementary Table S33)) and moderate accuracy to predict AKI (AUC 0.80) and Stage 2 to 3 AKI (AUC 0.85) in children (5 studies;[16] Supplementary Table S34). L-FABP has been approved as a clinical biomarker for AKI in Japan, where it is routinely available in clinical laboratories.

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Limiting use to biomarkers with demonstrated clinical validity and regulatory approval ensures reliable interpretation and performance in appropriate patient populations.[2, 4-6] When applied in acute care settings where AKI risk is high, these biomarkers can enhance risk stratification, support more proactive care, and improve alignment of preventive interventions with patient risk. No single biomarker has utility for the prediction or early detection of AKI across all clinical settings (Table 4).

Potential harms from biomarker measurement include false-positive results that may lead to unnecessary monitoring, interventions, patient and family anxiety, as well as false-negative results that could provide false reassurance if over-relied upon. In the absence of clearly defined action pathways, positive biomarker results (like SCr alerts) may also prompt over-escalation of care (e.g., additional monitoring or higher-acuity placement) without clear benefit. Additional considerations include variability in biomarker performance across populations and settings, and the risk of inappropriate use outside validated indications. However, when biomarkers are used selectively, interpreted in conjunction with clinical assessment, and applied according to approved indications, the anticipated benefits of earlier and more targeted prevention strategies are judged to outweigh the generally low and manageable risks related to imperfect performance.

Certainty of evidence

The certainty of evidence for implementing urinary [TIMP-2]*[IGFBP7] testing in adults undergoing major surgery is moderate based on RCT data.[2, 4-6] RCTs evaluating urinary [TIMP-2]*[IGFBP7]-based care were downgraded for methodological issues due to lack of blinding, but were consistent and provided a precise estimate to reduce risk of Stage 2–3 AKI. Other populations (e.g., people in the ICU) have not been systematically evaluated; thus, the certainty of evidence is downgraded for other populations. Further supporting the recommendation, overall, studies provided low certainty of evidence of predictive accuracy for Stage 2–3 AKI in adults.[218] These studies had some methodological limitations and provided imprecise estimates of test accuracy.

No RCTs of urine [TIMP-2]*[IGFBP7] testing have been conducted in children. Regarding diagnostic accuracy, the certainty of evidence in children is moderate that [TIMP-2]*[IGFBP7] has low to moderate accuracy (defined as AUC between 0.76 and 0.85) to predict AKI-related outcomes.[16] The certainty of evidence was downgraded for methodological limitations of the studies to predict incident AKI and Stage 2–3 AKI, with imprecision regarding prediction of RRT and mortality. However, without trial evidence in children, the certainty of evidence for implementing urinary [TIMP-2]*[IGFBP7] testing in children was downgraded to low.

RCTs have not evaluated implementing urine NGAL testing in either adults or children. In adults, there is moderate certainty of evidence that urine NGAL has low-to-moderate sensitivity and moderate specificity to predict AKI outcomes (low sensitivity or

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specificity defined as 51-75% and moderate sensitivity or specificity defined as 76%–89%).[218] The certainty of evidence was downgraded for methodological limitations of the studies. Estimates of test accuracy to predict Stage 2–3 AKI and RRT were imprecise. In children, there is moderate certainty of evidence that urine NGAL has moderate accuracy to predict AKI outcomes and mortality.[16] The certainty of evidence was downgraded for methodological limitations of the studies. Without trial evidence, the overall certainty of evidence for implementing urine NGAL testing was downgraded to low due to indirectness for adults and low for children.

RCTs have not evaluated implementing urinary KIM-1 testing in either adults or children. In adults, there is moderate certainty of evidence that urinary KIM-1 has moderate accuracy (as defined above) to predict incident AKI, but no evidence regarding prediction of more severe AKI. In children, there is also moderate certainty of evidence regarding test accuracy of urinary KIM-1.[16] Specifically, there is moderate certainty of evidence for prediction of incident AKI and mortality, due to study limitations, but there is only low certainty of evidence for prediction of Stage 2–3 AKI or RRT (further downgraded for imprecision). Without trial evidence, the overall certainty of evidence for implementing urinary KIM-1 testing was downgraded to low due to indirectness for both children and adults.

RCTs have not evaluated implementing urinary L-FABP testing in either adults or children. In adults, there is moderate certainty of evidence that urinary L-FABP has low sensitivity and moderate specificity (as defined above) to predict incident AKI in adults, in addition to moderate accuracy to predict incident AKI or severe AKI in children. The certainty of evidence was downgraded for methodological limitations. Without trial evidence, the overall certainty of evidence for implementing urinary L-FABP testing was downgraded to low due to indirectness for both children and adults.

Values and preferences

Well-informed patients, caregivers, and healthcare professionals generally place a high value on early recognition of risk, particularly when progression to severe AKI may lead to significant morbidity, need for RRT, or prolonged hospitalization. The use of validated biomarkers of kidney stress or damage in combination with clinical assessment aligns with this value by offering earlier and more objective information than traditional measures alone, supporting timely and proactive kidney-protective care in high-risk acute care settings.

Preferences may vary regarding the use of additional testing, especially if results will not clearly change management or if there is uncertainty about interpretation. Some patients and caregivers may prioritize minimizing tests, costs, or anxiety associated with abnormal results. Healthcare professionals may also differ in their comfort and familiarity with

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biomarker-guided strategies. These variations in values and preferences support a Level 2 statement, emphasizing selective use according to validated indications.

Resource use and cost

Use of additional biomarkers entails additional direct costs related to setting up the laboratory assays as an in-house test to provide timely results, as well as per test costs. These costs vary by biomarker, testing frequency, and local laboratory infrastructure, and are higher than those of conventional kidney function tests. Implementation may also require investment in healthcare professional education, protocol development, and integration of results into clinical workflows or EHRs to ensure appropriate use of results. In high-resource settings, where laboratory infrastructure, regulatory approval, and supply chains are established, biomarker testing can be integrated into routine workflows with predictable per-test costs and rapid turnaround times. In low-resource settings, limited access to biomarker assays, higher relative costs, lack of analyzer platforms, or longer turnaround times may substantially increase resource burden or make testing not feasible. In such contexts, routine biomarker use could divert resources from other essential aspects of care without clear added value. Selective or restricted use, when available, may be more appropriate, and reliance on clinical assessment and conventional tests may remain the primary strategy.

Biomarker-guided risk stratification may lead to more efficient use of healthcare resources by enabling targeted kidney-protective strategies in people most likely to benefit, while avoiding unnecessary interventions in those at lower-risk. Earlier identification of people at risk of severe AKI has the potential to reduce downstream costs associated with AKI complications; however, findings from cost-effectiveness analyses have been highly uncertain.[222] The BigpAK trial reported a reduction in overall cost of care following implementation of [TIMP-2]*[IGFBP7] measurement through improved AKI care processes and shorter lengths of stay.[5] Thus, while upfront testing costs are higher, emerging evidence suggests that selective use according to validated and approved indications may result in a favorable balance between resource use and clinical value in some settings (e.g., following major surgery).

Cost-effectiveness is likely to depend on baseline AKI risk/incidence in the tested population and whether biomarker results are linked to an actionable intervention and thus may vary substantially across clinical settings and health systems.

Considerations for implementation

Accessibility and availability of biomarker tests are important considerations for implementation, particularly across settings with varying resource levels.[223] In high-resource settings, these tests may be readily available with rapid turnaround times and electronic integration, facilitating timely risk stratification and protocolized kidney-protective responses. In contrast, limited laboratory infrastructure, higher costs, and lack of regulatory

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approval restricts availability in low-resource settings, making routine or widespread use challenging.

Implementation strategies should therefore be tailored to local capacity; prioritizing biomarker use in clinical scenarios where the added prognostic value is greatest and where results can realistically influence management. Clear protocols should define appropriate indications, timing of testing, and thresholds for action to ensure biomarkers are used consistently and inform management. Healthcare professionals and healthcare teams should receive training on the appropriate interpretation of biomarker results and their limitations, emphasizing biomarkers as adjuncts to, rather than replacements for, clinical assessment.

To implement biomarker testing safely, centers should predefine eligibility criteria and a targeted testing strategy (i.e., who is tested, when, and how often) focusing on high-risk populations to avoid indiscriminate testing and over-response. Biomarker results should be linked to a standardized kidney-protective management strategy (e.g., closer urine output /SCr monitoring, medication review/avoidance of nephrotoxins where feasible, and hemodynamic/volume reassessment, with early nephrology consultation or RRT preparedness when appropriate). Because access and performance may vary across settings and patient subgroups, programs should also evaluate availability and test performance across key subgroups to support transportability and avoid widening disparities.

Rationale

There is evidence that selected biomarkers of kidney stress or damage can identify people at increased risk of developing severe AKI 12–24 hours earlier than traditional markers and can provide opportunities to implement targeted kidney-protective strategies and improve outcomes. It is essential that appropriate biomarkers are chosen for specific clinical settings and interpreted accordingly.

This recommendation is supported by evidence that tubular stress/damage biomarkers can identify people at increased risk of subsequent severe AKI at an earlier stage, and by a limited body of randomized trial data showing that selection of patients based on biomarker criteria followed by application of kidney-protective interventions can reduce AKI in selected surgical populations; however, evidence that care delivery with biomarker testing versus without improves patient-centered outcomes is lacking. Knowledge of effective implementation strategies in broader non-surgical settings remain limited.

2.5. Tests for AKI etiology and diagnostic evaluation

Recommendation 2.5.1. In adults with AKI, we suggest urine microscopy as part of the diagnostic evaluation, particularly when the etiology is unclear or intrinsic kidney disease is suspected, as urine sediment examination can provide diagnostic and prognostic information that complements clinical assessment and other laboratory studies *(2D)*.

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This recommendation places a high value on diagnostic accuracy, clinical insight, and avoidance of unnecessary or inappropriate interventions in the evaluation of AKI. Urine microscopy is a noninvasive, low-cost test that can provide direct information about kidney pathology and prognosis, which can influence patient management. The Level 2 strength of this statement reflects the fact that the value of urine microscopy will differ depending on individual patient circumstances and that access to healthcare professionals trained in urine microscopy may be limited in many centers.

Key information

Balance of benefits and harms

Urine microscopy is a diagnostic tool used to examine concentrated urine sediment to identify features suggestive of acute tubular injury (ATI), glomerular disease, acute interstitial nephritis (AIN), and crystal-associated AKI, thereby refining the differential diagnosis of AKI. Specific sediment findings may also provide prognostic information, as they have been associated with AKI severity and risk of progression. Identification of diagnostic sediment features may prompt earlier targeted evaluation or treatment, including appropriate use of serologic testing, avoidance of unnecessary therapies, or consideration of kidney biopsy.

Granular casts have moderate sensitivity and high specificity to predict AKI, and 100% specificity and 100% positive predictive value for prediction of ATI. Granular casts were associated with a ≥50% increase in creatinine from baseline at discharge. A study in 661 participants who underwent noncardiac surgery and were admitted to the ICU showed that urine microscopy scores based on epithelial cells, renal tubular epithelial cells, and granular casts had high specificity with low sensitivity for ATI (Supplementary Table S35).[224]

The principal limitations of urine microscopy relate to access to nephrologists with expertise in urine sediment evaluation, operator dependence, and variability in expertise, which reduce reproducibility and diagnostic accuracy. Misinterpretation of urine sediment findings may lead to diagnostic uncertainty or inappropriate downstream testing and treatment if results are not integrated with the overall clinical context. Given its absence of procedural risk, the potential clinical benefit is considered meaningful, particularly in people with unexplained AKI or suspected intrinsic kidney disease.

Certainty of evidence

Based on 3 studies conducted in adults, each evaluating different features or scoring systems based on urine microscopy, there is low certainty of evidence that the urinary microscopy score in people undergoing noncardiac surgery admitted to the surgical ICU has high specificity to predict that patients will not develop Stage 2–3 AKI;[224] very low certainty of evidence that muddy brown granular casts have moderate sensitivity and high specificity

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for predicting ATI in people with Stage 2–3 AKI;[225] and very low certainty of evidence that in people with AKI, absence of urine eosinophils has high specificity to predict that people do not have acute interstitial nephritis.[226] The certainty of evidence for each measure was downgraded for sparseness of data; although, both studies evaluating urinary microscopy score and urinary eosinophils were large. Because there is no trial evidence about the clinical effect of implementing urine microscopy, the overall certainty of evidence was downgraded to very low for each urine microscopy measure in adults.

Values and preferences

Urine microscopy carries minimal risk and thus well-informed patients and healthcare professionals are likely to place a high value on its use when it may inform diagnosis, prognosis, and management. Potential downstream testing or treatment decisions prompted by urine microscopy findings are expected to be guided by clinical judgment, thereby limiting unnecessary interventions. There is variability in expertise, availability, and interpretive skill across clinical settings. Thus, its value depends on appropriate performance, interpretation, and integration with the broader clinical picture. Overall, most patients and healthcare professionals are expected to favor the use of urine microscopy when performed and interpreted appropriately, given its minimal burden and potential to improve the understanding of the cause and likely course of AKI.

Resource use and costs

Urine microscopy is a low-cost diagnostic test that can be performed using existing laboratory infrastructure in most healthcare settings. Required resources are limited to standard microscopy equipment and services of trained personnel for specimen preparation and interpretation. It is, however, labor intensive because a skilled nephrologist is usually needed to analyze a fresh urine sample. However, when the etiology of AKI is unclear or an intrinsic kidney disease is suspected, the cost is generally small relative to the value of the information it can provide.

Urine microscopy may help optimize downstream resource use by guiding more targeted diagnostic testing, avoiding unnecessary interventions, and supporting timely management decisions. However, availability of trained personnel may be limited in some institutions. Also, in some countries, special certification is needed to record the results but overall the additional resource requirements of the test are modest.

Considerations for implementation

Successful implementation of this recommendation requires adequate healthcare professional or laboratory expertise in identifying and interpreting the urinary sediment. Training healthcare professionals in microscopy technique and interpretation is important to ensure accurate and reproducible results. Standardization of protocols and reporting of sediment evaluation may facilitate more consistent interpretation by healthcare professionals. In many settings local expertise and access to nephrology services is limited, which presents

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a barrier to routine incorporation into clinical evaluation for AKI, particularly in less resourced and remote centers. Abnormal findings from initial urine dipstick testing may identify people in whom further evaluation with urine microscopy evaluation is warranted. When access is limited, integration into clinical workflow should emphasize selective use, focusing on people in whom the etiology of AKI is unclear or an intrinsic kidney disease is suspected. Where nephrology expertise is limited, institutions may consider standardized lab-based protocols with periodic competency assessment and structured reporting.

Because urine microscopy (including urine microscopy scoring) is low-cost, it may be particularly useful in resource-limited settings; however, test performance depends on trained personnel and standardized reporting, and automated urinalysis systems may miss key sediment findings relevant to tubular injury.[227]

The strength of recommendation is Level 2 reflecting the anticipated variation in healthcare professional experience, availability of institutional resources, and patient-specific value of the test.

Rationale

Urine microscopy allows direct visualization of urinary sediment and can provide important insights into the underlying pathophysiology of AKI (Table 18). Specific sediment findings, such as renal tubular epithelial cells and granular casts, support a diagnosis of ATI.[228] Findings such as dysmorphic red blood cells or red blood cell casts suggest glomerular disease, and white blood cells or white blood cell casts may support AIN, prompting targeted diagnostic evaluation and consideration of kidney biopsy.[229] The absence of pathologic findings (i.e., a bland sediment) may support a hemodynamic-mediated process, although it does not exclude early or evolving structural injury. Although supporting studies were conducted in adults, the pathophysiologic basis for urine sediment findings is not age dependent. The cellular and cast elements that reflect ATI, glomerular disease, or interstitial nephritis are shared across pediatric and adult populations.

Manual urine microscopy should be performed by trained personnel using standardized procedures to ensure reliable results for patient care.[230] Limitations include operator dependence and variability in expertise.[231] Automated urinalysis is time saving, standardized, and commonly used due to efficiency and cost, but have not been demonstrated to be sufficiently reliable to identify ATI, glomerulonephritis, or interstitial nephritis. Therefore, healthcare professionals are advised not to rely solely on laboratory-reported urinalysis for clinical diagnosis and decision-making, although findings on an initial urinalysis may prompt further evaluation by manual urine microscopy.

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Table 18 | Urine sediment and associated kidney injury syndromes

Syndrome	Urine sediment	Urine dipstick
Hemodynamic-mediated (prerenal) AKI	Bland, hyaline casts, few finely granular casts, occasional RTECs	−/+ protein
Acute tubular injury (ATI)	RTECs, RTEC casts, course granular casts, "muddy brown" casts	−/+ protein
Acute interstitial nephritis (ATN)	WBCs, WBC casts, RTECs, RTEC casts, RBCs, occasional RBC casts	−/+ protein,+/++ LE, +/++ blood
Nephritic syndrome	Dysmorphic RBCs (acanthocytes), isomorphic RBCs, WBCs, RBC casts, WBC casts	+/++ protein, ++/+++ blood
Nephrotic syndrome	Lipid droplets, oval fat bodies, birefringent Maltese cross, lipid laden casts, cholesterol crystals	+++/++++ protein
Crystalline nephropathy	Various endogenous or drug-related crystals, RTECs, RBCs, WBCs, some WBCs engulfing crystals	−/+ blood, −/+ LE
Osmotic nephropathy	Swollen RTECs with cytoplasmic vacuoles, RTEC/granular casts	−/+ protein

LE, leukocyte esterase; RBCs, red blood cells; RTECs, renal tubular epithelial cells; WBCs, white blood cells. Reproduced from Cavanaugh 1, et al. 2019.[230]

Practice Point 2.5.1: Muddy brown granular casts and renal tubular epithelial cells can assist in distinguishing acute tubular injury (ATI) from hemodynamic-mediated AKI and predict progression to severe AKI.

Muddy brown granular casts and renal tubular epithelial cells (RTEC) have long been associated with ATI. In a biopsy-anchored study, granular casts were consistently observed in 49 participants with histologically confirmed acute tubular necrosis (ATN) the histopathologic correlate of ATI, with 100% specificity and positive predictive value, and with moderate sensitivity of 78% for a biopsy diagnosis of ATN (Supplementary Table S36).[225]

A number of standardized scoring systems (urine microscopy or sediment scores) have been developed to quantify casts and RTECs and help with diagnosis and prognostication of AKI. Perazella *et al.* developed and examined the utility of a urinary scoring system based on RTECs and granular casts in 231 participants with hospital-acquired AKI.[228] The likelihood ratios for ATI increased as the number of granular casts or RTECs (and score) increased. In participants with a pretest diagnosis of ATI, the presence of any casts or RTEC (urine sediment score ≥2) had a positive predictive value of 100% for a final diagnosis of ATI. In participants with a pretest diagnosis of "prerenal" AKI, the lack of granular casts or a urine sediment score of 0 had a negative predictive value of 91% for a final diagnosis of "prerenal" AKI. Using an AKI scoring index developed by Chawla *et al*., a score ≥2 (reflecting at least 1 cast or RTEC seen but in <10% of low power fields) predicted non-recovery of kidney function.[232] A modified score by Perazella, was used to evaluate the outcome of worsening AKI (higher stage, RRT requirement, or death) in 197 participants with AKI. When compared to a urinary score of 0, a score of ≥3 was associated with a 7-fold greater adjusted risk of worsening AKI (risk ratio [RR]: 7.3; 95% CI: 3.8–9.6). In a study of

661 participants following cardiac surgery, a urine microscopy score ≥3 at 6 hours after ICU admission carried high specificity (98%) but low sensitivity (5%) for severe (Stage 2 or 3) AKI.[224] Moreover, elevated scores were independently associated with greater odds of postoperative complications and longer ICU stay.

In a prospective cohort of non-ICU hospitalized adults at moderate-to-high risk of AKI, an admission urine microscopy score (UMS) provided a structured measure of tubular injury (UMS ≥2 identifying 'subclinical AKI') and showed good discrimination for clinical AKI within 48 hours (AUC ~0.84), with higher UMS also associated with subsequent RRT use and mortality.[232]

Urine microscopy demonstrates prognostic utility over clinical assessment alone. Hall *et al*. evaluated urine microscopy score and newer urine biomarkers in 249 hospitalized participants with AKI. The adjusted risk of the primary outcome of worsened AKI or death was approximately 3 times greater in participants in the higher versus the lowest groups of urinary biomarker levels (NGAL, KIM-1, and IL-18) as well as urine microscopy score. Net reclassification significantly improved with the addition of both newer biomarkers or urine microscopy to clinical variables, suggesting that urine microscopy may be as useful as newer biomarkers to improve risk stratification of AKI.

Practice Point 2.5.2: Urine eosinophil testing has low sensitivity and moderate specificity, limiting its diagnostic value particularly for excluding a diagnosis of acute interstitial nephritis (AIN).

Acute interstitial nephritis is a cause of AKI characterized by an inflammatory infiltrate in the kidney interstitium.[233] While AIN has multiple potential etiologies, drugs are the most common causes (70%), with antibiotics accounting for 30%–50% of cases.[233-235] Proton pump inhibitors (PPIs) have also been associated with AIN and appear to play a role in increasing the risk of immune-check point inhibitor-associated AIN.[235, 236] AIN is important to diagnose because it is a common, often reversible cause of AKI where early recognition and targeted treatment can prevent permanent kidney damage.

In an early study, 65 of 470 (16%) participants with AKI were reported to have urine eosinophils on examination of the urinary sediment.[237] Of these 65 participants, only 9 (14%) had a final diagnosis of AIN. The incidence of AIN was higher in those with >10% urine eosinophils (4 of 7 participants) and AIN was diagnosed in 4 of 10 participants with urine eosinophils >5%. In the ensuing 3 decades, several case series suggested that elevated urine eosinophils might be considered diagnostic of AIN, although thorough diagnostic accuracy studies to confirm this hypothesis have been lacking. In 2013, a retrospective case series of 566 participants with urine eosinophils measured within 7 days of a kidney biopsy showed that 91 participants had AIN.[226] When looking at the test performance of both a 1% and 5% urine eosinophil cutoff, a cutoff of 1% provided a sensitivity of 31% and specificity of 68%

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for the diagnosis of AIN. When using the 5% cutoff, the sensitivity was lower at 20% and specificity was higher at 91% (Supplementary Table S37). There was no meaningful difference in operating characteristics when these same cutoffs were applied to cases with ATN. Thus, even at a cutoff of 5%, absence of urine eosinophils has limited ability to rule out AIN from other forms of AKI, limiting their utility as a diagnostic test for AIN, particularly for excluding the diagnosis in routine clinical care.[226, 238]

Urine eosinophils are neither necessary nor sufficient to diagnose AIN and routine testing for urine eosinophils for the diagnosis of AIN is not advisable. When clinical suspicion of AIN is high, a definitive evaluation (including kidney biopsy when appropriate) and timely initiation of indicated therapy should not be delayed.

Practice Point 2.5.3: Urinary inflammatory cytokines may be useful in distinguishing AIN from other causes of AKI or AKD in adults.

Emerging evidence indicates that detection of inflammatory cytokines in urine may help distinguishing AIN from other mechanisms of AKI. Among people with AIN diagnosed by kidney biopsy, both urinary IL-9 and urinary TNF-α levels were higher in those with AIN compared with other types of AKI, with an AUC of 0.83 (95% CI: 0.73–0.92).[239, 240] Chemokine C-X-C motif ligand (CXCL) 9 (CXCL9), an interferon gamma induced chemokine involved in lymphocyte chemotaxis, has also been evaluated as a urinary biomarker of AIN.[241] In preclinical and human studies CXCL9 levels were higher in people with kidney biopsy proven AIN, with nearly 4-fold higher microRNA tissue expression of the chemokine when AIN was present. In the original cohort of 204 participants with kidney biopsies, of whom 15% had biopsy-proven AIN, participants with urine CXCL9 levels in the highest quartile had an adjusted OR of 6.0 (95% CI: 1.8–20.0) for AIN when compared to those in the lowest quartile. In a validation cohort, urinary CXCL9 provided an AUC of 0.94 (95% CI: 0.86–1.00) for the diagnosis of AIN with levels being over 7.5 fold higher in participants with AIN compared to those with other biopsy findings (p=0.00001).[241]

In a longitudinal study of participants with AIN, there was a statistically significant decrease in 6-month GFR in participants with urinary IL-9 levels above the median of 0.66 ng/g compared with those with lower IL-9 values (p=0.005) among participants who did not receive corticosteroids.[242] The study also showed that corticosteroid use was associated with higher 6-month GFR compared to no corticosteroids only when urinary IL-9 >0.66 ng/g (p=0.05), suggesting that urinary IL-9 levels can help identify people who might benefit from corticosteroids.[242] Elevated urinary TNF-α was also found to be associated with AIN over other types of AKI among participants on immune checkpoint inhibitor therapy [AUC: 0.81; 95% CI: 0.62−1.00).[243] Urinary cytokines including interferon-inducible T cell alpha chemoattractant (I-TAC)/CXCL11 (I-TAC/CXCL11), CXCL10, interleukin-6 (IL-6), and monocyte chemotactic protein-1 (MCP-1) have also shown potential diagnostic value in diagnosing AIN.[244] Detection of elevated concentrations of urinary cytokines may change

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management by prompting kidney biopsy and/or corticosteroid treatment for AIN; however, clinical implementation of this approach depends on availability of local laboratory assays and test validation. In addition to limited availability and lack of assay standardization, urinary cytokine levels may be confounded by other inflammatory kidney diseases and intercurrent infection (e.g., urinary tract infection) and therefore should be interpreted in clinical context.

Practice Point 2.5.4: Urine chemistries, including fractional excretion of sodium (FeNa) and fractional excretion of urea (FeUrea) should be reserved for use in differentiating hemodynamic-mediated (prerenal) AKI from ATI in selected clinical scenarios and groups of children and adults with AKI, due to their limited overall clinical utility.

Urine chemistries, including FeNa and FeUrea, have historically been used to support differentiation between hemodynamic-mediated (prerenal) AKI and ATI (ATN). Traditionally, low FeNa (<1%) and FeUrea (<35%) were considered indicative of prerenal AKI in older children and adults who had oliguria, were not on diuretics (for FeNa), and were without a history of CKD. However, contemporary evidence indicates that these indices have limited diagnostic performance when applied in the majority of people with AKI,[245] in whom the physiologic assumptions underlying FeNa and FeUrea (preserved tubular sodium and urea handling in hemodynamic-mediated AKI) are often not met, and confounding factors, including diuretic exposure, CKD, and recent fluid or vasoactive therapy are often present.[246]

A systematic review and meta-analysis from 2022 identified 19 studies comprising 1287 participants that examined the accuracy of FeNa for differentiating prerenal versus intrinsic AKI.[247] Among 15 studies using the conventional FeNa threshold of 1%, the pooled sensitivity was 90% (95% CI: 81%–95%; I^2: 85%), and pooled specificity was 82% (95% CI: 70%–90%), I^2: 82%.[247] Importantly, when examining the subset of 8 studies, including 264 participants who were oliguric, not exposed to diuretics, and without CKD, the 1% threshold showed very high diagnostic accuracy, with sensitivity of 95% (95% CI: 82%–99%) and specificity of 91% (95% CI: 83%–95%). In contrast, among 6 studies that included 511 participants who had CKD or were on diuretics, the sensitivity and specificity dropped substantially to 83% (95% CI: 64%–93%) and 66% (95% CI: 51%–78%), respectively.[247]

Although FeUrea has been proposed as an alternative for people receiving diuretics, observational studies demonstrate wide variability and overlap in FeNa and FeUrea values among people with hemodynamic-mediated AKI and tubular injury, reducing their reliability for etiologic classification and limiting their influence on clinical decision-making.[248-251] In most people, clinical context, trajectory of kidney function, urine sediment examination, and biomarkers of tubular stress or damage provide more insight into AKI pathophysiology than urine chemistries alone.

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Practice Point 2.5.5: In adults with cirrhosis-associated AKI, FeNa can be an adjunctive tool to distinguish hepatorenal syndrome from ATI when interpreted in the appropriate clinical context.

Cirrhosis-associated AKI encompasses a heterogeneous group of pathophysiologic processes, including hepatorenal syndrome, ATI, and mixed or overlapping phenotypes. Differentiating hepatorenal syndrome from ATI has important therapeutic and prognostic implications, particularly with respect to the use of vasoconstrictor therapy, albumin administration, and decisions regarding RRT and liver transplant evaluation.[252]

FeNa may retain discriminatory value in cirrhosis, owing to the distinct renal sodium-handling physiology characteristic of hepatorenal syndrome. Hepatorenal syndrome is marked by intense renal vasoconstriction with preserved tubular integrity, resulting in avid sodium retention and typically very low FeNa values. In comparison, ATI in cirrhosis is associated with structural tubular damage, impaired sodium reabsorption, and relatively higher FeNa values.

Several observational studies have demonstrated that very low FeNa values (often <0.1%–0.2%) are more consistent with hepatorenal syndrome, whereas higher values increase the likelihood of tubular injury,[246, 253] particularly when supported by additional clinical and laboratory features (e.g., urinary sediment, lack of response to volume expansion, exposure to nephrotoxins, or ischemic insults). However, important limitations should be recognized. FeNa values may be affected by diuretic exposure, recent volume administration, sepsis or systemic inflammation. Further, mixed hepatorenal syndrome–ATI phenotypes are common in advanced cirrhosis.[252, 254, 255] Still, in studies comparing FeNa with FeUrea in people with liver disease, FeNa consistently outperformed FeUrea for distinguishing hepatorenal syndrome from other forms of AKI.[256, 257]

Accordingly, FeNa should not be used in isolation to establish the diagnosis of hepatorenal syndrome or ATI. Rather, it should be interpreted alongside clinical criteria for hepatorenal syndrome, urine sediment findings, and the overall clinical trajectory. The Work Group agreed with consensus statements from the International Club of Ascites (ICA) and the ADQI emphasizing that while urinary indices such as FeNa may provide supportive data, diagnosis of hepatorenal syndrome should not rely solely on these values due to their variable sensitivity and limited specificity in complex clinical settings.[252, 258]

Practice Point 2.5.6: In adults with cirrhosis-associated AKI, urinary or plasma NGAL may be an adjunct to help differentiate between ATI and hepatorenal syndrome, particularly when clinical features or response to volume expansion or vasoconstrictor therapy are equivocal.

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Biomarkers that offer direct assessment of tubular injury may be adjuncts in diagnostic evaluation with implications for management. NGAL has been relatively extensively studied as a biomarker in cirrhosis-associated AKI.[246, 253] In a multicenter, prospective observational study by Belcher *et al.*, 188 participants with cirrhosis and AKI were adjudicated by an expert panel as having prerenal AKI (n=55), hepatorenal syndrome (n=16), or ATI (n=39).[246] Urine NGAL levels were significantly higher in ATI (565 ng/ml; IQR: 76–1000) than in hepatorenal syndrome (115 ng/ml; IQR: 51–373) and prerenal AKI (54 ng/ml; IQR 17–180; p <0.001), providing early evidence that NGAL could assist in distinguishing the cause of AKI in people with cirrhosis.[217, 259]

A subsequent, larger prospective multicenter study evaluated 213 hospitalized participants with decompensated cirrhosis, 161 of whom had AKI. Of these, 57 had volume-responsive AKI, 55 met ICA criteria for hepatorenal syndrome, and 49 had ATI. NGAL levels normalized to urine creatinine followed a similar pattern: lowest in prerenal AKI (45 µg/g creatinine; IQR: 0–154), intermediate in HRS (110 µg/g creatinine; IQR: 50–393), and highest in ATI (334 µg/g creatinine; IQR 132–1429; p <0.001).[260] NGAL discriminated ATI from other AKI types with a C-statistic of 0.76 (95% CI: 0.68–0.84), a positive predictive value of 56%, and a negative predictive value of 86%. Urinary NGAL also independently predicted overall and transplant-free survival, modestly outperforming the Model for End-Stage Liver Disease (MELD) score. A systematic review and meta-analysis aggregating multiple cohorts (21 studies, n=3701 participants) reported a pooled duration of response of 22.15 (95% CI: 17.58–27.89) for the ability of urine NGAL to detect ATI.[261]

These results suggest that NGAL is a useful tool for diagnosing and predicting outcomes in cirrhosis-related AKI, especially when clinical signs, response to volume, or changes in creatinine are unclear. However, AKI in cirrhosis is often multifactorial, and individual patients may exhibit overlapping features of volume depletion, hepatorenal syndrome, and ATI. Further, NGAL assays are unavailable in many centers, thresholds for NGAL interpretation vary by assay, and NGAL has not been incorporated into formal diagnostic criteria for hepatorenal syndrome. Thus, when used, NGAL should be integrated with clinical findings, urine sediment examination, therapeutic response, and longitudinal assessment of kidney function to support clinical decision-making in selected patients.[209, 262]

Practice Point 2.5.7: Kidney biopsy should be considered for children and adults with unexplained AKI when clinical evaluation does not clearly differentiate among potential causes or the findings are expected to influence management decisions.

Kidney biopsy may be considered in people with unexplained AKI when clinical evaluation does not clearly differentiate among potential etiologies or when histopathological diagnosis is expected to influence clinical decision-making. While many cases of AKI can be managed based on clinical and laboratory data alone, a subset of people present with diagnostic uncertainty, atypical presentations, or nonresolving injury, where biopsy may

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provide crucial insights that guide management. Biopsy findings can clarify ambiguous presentations, identify treatable diseases, prevent therapeutic misdirection, and enable personalized care.

Studies have consistently shown that histologic diagnoses obtained from kidney biopsies for AKI can diverge from clinical impressions. In a large study conducted in the 1990s in the U.S. of 259 older adults who received a native kidney biopsy for AKI, biopsy yielded a definitive diagnosis in over 90% of cases, kidney biopsy diagnosis differed from the prebiopsy clinical diagnosis in 33% of cases, and a diagnosis offering the potential for improved outcomes with treatment was deemed to have been made in 73% of the cases.[263] Kidney biopsy findings also provide prognostic information. In a Korean multicenter cohort, biopsy-confirmed ATN and AIN had distinct outcomes, with AIN conferring a higher risk of progression to kidney failure.[264]

Regional biopsy series further highlight the diagnostic value of histopathologic assessment. In a case series of patients biopsied for AKI from a tertiary care center in South India, AIN was the most commonly diagnosed lesion.[265] A systematic review by Wen *et al*. confirmed significant diversity in the histopathologic manifestations of ATI and noted limited correlation with clinical phenotypes.[266] In the setting of COVID-19, biopsies have revealed a wide spectrum of kidney pathologies, including collapsing glomerulopathy, ATN, and minimal change disease, which were not clinically apparent.[267, 268] This diagnostic variability highlights the limitations of relying solely on noninvasive assessments in complex or diagnostically uncertain clinical scenarios.

The Kidney Precision Medicine Project (KPMP) reinforces the diagnostic value of biopsy, to integrate kidney tissue analysis with molecular and clinical data, demonstrating significant pathologic and transcriptomic heterogeneity in AKI, even among clinically similar patients.[269] These findings support broader use of kidney biopsy, helping to uncover disease sub-endotypes and potential therapeutic targets.[270] Biopsy is particularly critical when etiologic certainty is important for subsequent management decisions, such as with immune checkpoint inhibitor associated AKI. A case series by Rashidi *et al*. illustrated presentations where people with presumed AIN based on clinical grounds had ATI on biopsy, which allowed continuation of oncologic immunotherapy and avoided inappropriate change of immunosuppression.[271]

Concerns around procedural risks of kidney biopsy must be balanced against diagnostic and therapeutic yield. A meta-analysis of over 118,000 native kidney biopsies reported low rates of significant complications, such as major bleeding (0.3%) and death (0.06%).[272] A multicenter, ICU-based study that included biopsies of 68 native kidneys (87% using ultrasound guidance), showed that a specific diagnosis other than ATN was established in 35 (51%) critically ill participants, and altered management decisions in 14 (21%) participants.[273] Biopsy complications occurred in 22% of participants of whom only 2 were

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graded as severe (requirement for kidney embolization). Although major complications after native kidney biopsy are uncommon in the general inpatient and outpatient populations, complication rates are higher in people who are critically ill and those undergoing biopsy in the ICU, where hemodynamic instability, coagulopathy, and greater illness severity are more frequent.

Practice Point 2.5.8: Kidney Doppler ultrasound, including measurement of renal resistive index (RRI), may aid in risk stratification for AKI progression and severity, particularly in critically ill populations.

Kidney ultrasound using Doppler technique, specifically with measurement of renal resistive index (RRI) and renal pulsatility index (RPI) has emerged as a noninvasive diagnostic adjunct for predicting the development of AKI, especially in the ICU setting.[274, 275] The RRI reflects downstream resistance in the renal arterial vasculature and is calculated from systolic and diastolic velocities in renal arteries. In the context of AKI, higher RRI values have been associated with renal hypoperfusion and vascular resistance that precedes SCr elevation. RRI is influenced by systemic hemodynamics and extrarenal factors (e.g., arterial compliance, heart rate, venous congestion, and intra-abdominal pressure) and should not be interpreted as a measure of intrinsic renal vascular resistance alone. Thus, Doppler ultrasound measurements of RRI (and optionally RPI) may be used as adjuncts for early prediction of AKI, alongside standard clinical and laboratory parameters.

Evidence review of data of 5 studies in a total of 572 critically ill adult participants showed that power doppler ultrasound had low sensitivity, but high specificity, with high overall accuracy to predict incident AKI.[276] Evaluation of RRI had moderate sensitivity, specificity and accuracy to predict AKI incidence with an AUC 0.83 (95 % CI: 0.80–0.86).

Data in pediatric populations are more limited. Based on data from 3 studies in a total of 188 children, RRI had variable test accuracy (AUC: 0.86; 95% CI: 0.46–0.98) and RPI also had variable test accuracy (AUC: 0.84; 95% CI: 0.36–0.98) to predict the risk of AKI across studies.[277-279]

Doppler ultrasound findings are operator-dependent, which is an important limitation. Standardization of threshold values and protocol integration is needed to support implementation in clinical settings.

Practice Point 2.5.9: In hospitalized or critically ill patients with AKI, point-of-care ultrasound (POCUS) may assist in assessing volume status and distinguishing volume responsive AKI from intrinsic AKI.

Ultrasound is a readily available, noninvasive test that can help identify potentially reversible causes of AKI. In selected people presenting with AKI who have risk factors,

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signs, or symptoms of urinary tract obstruction (e.g., anuria/oliguria, lower urinary tract symptoms, known or suspected stones, pelvic malignancy, benign prostatic hyperplasia, neurogenic bladder, prior urologic surgery, or an indwelling catheter with poor output), kidney and bladder ultrasound (KUB) should be considered to evaluate for hydronephrosis and bladder outlet obstruction, as these findings may prompt immediate, kidney-sparing interventions. In addition to excluding obstruction, bedside ultrasound can be integrated with point-of-care assessments to support hemodynamic evaluation in hospitalized and critically ill patients with AKI.

Clinical differentiation between volume-responsive and intrinsic AKI (with structural kidney damage) can be a diagnostic challenge, particularly in people with conditions that make clinical volume assessment difficult. POCUS has emerged as a valuable adjunct to physical examination, offering real-time, noninvasive insights into intravascular volume, venous congestion, and structural abnormalities.

Multiorgan POCUS assessing cardiac, lung, abdominal, and venous structures can aid AKI management by identification of volume overload, venous congestion, and cardiac dysfunction. The inferior vena cava collapsibility index (IVC-CI) is a particularly useful POCUS-derived parameter for assessing fluid responsiveness and identifying people at risk for hypotension. A more detailed framework for AKI classification using POCUS has been proposed by Varanasi *et al*., where hemodynamic AKI is assessed using IVC collapsibility, lung B-lines, and echocardiographic surrogates.[280] Obstructive causes such as hydronephrosis and bladder outlet obstruction can also be readily identified at the bedside.

POCUS has been increasingly incorporated into management of AKI. In people who are critically ill with cirrhosis and hepatorenal syndrome, POCUS has been described to assess fluid status, cardiac function, and venous congestion, thereby influencing decisions around albumin therapy and vasopressor use.[281] Operator dependency is the major limitation.

Multiorgan POCUS is most informative when performed using a standardized protocol to assess volume status, venous congestion, and fluid responsiveness, and when supported by structured training, competency assessment, and ongoing quality assurance.

2.6. Considerations specific to children

Practice Point 2.6.1: Children at increased risk for community-acquired AKI should undergo a kidney health assessment during episodes of acute illness.

There are well-defined pediatric populations with a disproportionately high risk for AKI, such as solid organ transplant, malignancy, congenital heart disease, or CKD,, particularly during intercurrent illnesses.[282-284] Given the limited pediatric nephrology, workforce, expert groups have emphasized the importance of a structured kidney health assessment that can be implemented by pediatricians and other pediatric subspecialists to

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support risk stratification and identify children who may benefit from referral to a pediatric nephrologist.[285-288] Incorporating components of a kidney health assessment into the evaluation of high-risk children may facilitate early recognition of community-acquired AKI and timely interventions to mitigate progression and downstream morbidity (Table 19).

Table 19 | Components of kidney health assessment for risk stratification in high-risk children during acute illness

Component	Purpose
Serum creatinine	To assess kidney function and detect changes from baseline.
Urine output	To identify oliguria or anuria.
Urinalysis	To detect hematuria, proteinuria, or loss of concentrating ability
Electrolytes	To assess for hyperkalemia, hyponatremia, or metabolic acidosis
Fluid status assessment	To evaluate for signs of hypovolemia or fluid overload (e.g., edema, hypertension, respiratory distress), including weight changes, evaluation of fluid intake/output and assessment of capillary refill.
Medication review	To identify recent or ongoing exposures to potentially nephrotoxic agents and medications that may require dose adjustment in the setting of AKI.

AKI, acute kidney injury

Recommendation 2.6.1: For critically ill children at risk for AKI, we suggest using the renal angina index (RAI) to identify children at high risk of severe AKI and RRT *(2B)*.

This recommendation places a high value on early identification of children at increased risk of AKI and need for RRT who could benefit from closer monitoring of kidney function and damage markers, use of kidney-protective strategies, and particular attention to fluid balance management. This recommendation is based largely on test accuracy of the risk score for clinical outcomes (prediction of AKI, severe AKI, RRT, and mortality) without direct evidence of clinical effectiveness from "test and treat" study designs. Although test accuracy studies do not measure the impact of the RAI on patient management and outcomes, this Level 2 recommendation is based on the ability to apply kidney-protective strategies that are generally low-risk and low-cost, and to aid with planning for RRT for high-risk children.

Key information

Balance of benefits and harms

The RAI is a validated, bedside risk stratification tool that integrates readily available clinical risk factors (e.g., critical illness, mechanical ventilation, exposure to nephrotoxins with stem cell transplant) with early signs of kidney stress (e.g., changes in SCr or fluid overload; Table 20).

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Table 20 | Renal angina index scoring[289]

ICU admission alone	1 point
Solid organ or stem cell transplant	3 points
Ventilation or Inotropy	5 points
Kidney Injury or Volume overload • No decrease in eCrCl or < 5% FO • eCrCl decrease 0-25% or ≥5% FO • eCrCl decrease 25-50% or ≥10% FO • eCrCl decrease ≥50% or ≥15% FO	 1 point 2 points 4 points 8 points

eCrCl, estimated creatinine clearance; FO, fluid overload. Reproduced from Basu et al. 2014[289]

Evidence review of 18 studies in a total of 13,098 children showed that high RAI (≥8) has moderate accuracy to predict incident AKI (sensitivity 76%, specificity 78%) and Stage 2 to 3 AKI (sensitivity 85%, specificity 74%) within 48–72 hours, with moderate sensitivity (84%) but low specificity (61%) to predict need for RRT (Supplementary Table S38).[290-305]

Use of the RAI may support timely implementation of kidney-protective strategies, closer monitoring, and improved preparedness for potential RRT, which may reduce complications associated with delayed recognition of kidney failure. The high sensitivity of the RAI can be particularly helpful to identify children at low risk for severe AKI or RRT, potentially reducing unnecessary laboratory testing, invasive monitoring, or escalation of care. The index requires no invasive testing, is low cost, and feasible to implement in most inpatient settings, including intensive care units.

The potential harms of RAI use are limited. False-positive classification may lead to increased monitoring, additional blood tests, or additional intervention without clear evidence that these actions improve patient-centered outcomes. Such downstream effects may increase resource utilization. There is also a risk that reliance on the RAI could oversimplify complex clinical decision-making if used in isolation rather than in conjunction with clinical judgment. Overall, given the low likelihood of direct harm, the absence of invasive procedures, and the potential for clinical benefit through earlier identification of severe AKI and preparedness for RRT, the balance of benefits and harms favors use of the RAI and supports a Level 2 statement.

Certainty of evidence

There is high certainty of evidence that the RAI in children has moderate to high sensitivity (moderate defined as 76% to 89%, high defined as ≥90%) to predict AKI outcomes, including incident AKI and Stage 3 AKI, but with moderate certainty evidence, and poor specificity (defined as 51% to 75%) to predict RRT or death.[291-294, 296-303] The certainty of evidence for the latter outcomes was downgraded for methodological limitations of studies reporting Stage 2–3 AKI and for imprecision of estimates of specificity to predict RRT and mortality. No trials have evaluated the clinical impact of implementing the RAI in children; thus the overall certainty of evidence was downgraded, for indirectness, to moderate.

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Values and preferences

This recommendation places a high value on early identification of risk of severe AKI and need for RRT in critically ill children. Patients, families, and healthcare professionals generally prioritize strategies that reduce the risk of organ failure, invasive therapies, prolonged hospitalization, and long-term kidney disease, even when supported by low-certainty evidence, provided that the intervention is low risk. The moderate-to-high sensitivity of the RAI aligns with preferences to avoid unnecessary investigations or interventions in children at low risk, while focusing attention and resources on those most likely to benefit from closer monitoring or kidney-protective strategies.

Families may value the use of a transparent risk assessment tool that facilitates anticipatory guidance, earlier communication about potential kidney-related complications, and proactive care planning, including preparedness for possible RRT. At the same time, some families and healthcare professionals may place greater weight on avoiding over-monitoring or anxiety related to false-positive risk classification, particularly in the absence of definitive evidence that RAI-guided interventions improve outcomes. Thus, there is likely variability in how patients, families, and healthcare professionals weigh the benefits of early risk identification against the potential for increased monitoring and resource use. However, given the noninvasive nature of the RAI and the serious outcomes it seeks to prevent, most stakeholders would favor its use in children at risk for AKI, supporting a Level 2 statement.

Resource use and costs

Use of the RAI incurs minimal direct resource use as it is calculated using clinical variables that are routinely collected in standard inpatient care. Calculating and interpreting the RAI requires modest healthcare professional time, which may be integrated into routine assessments by physicians, nurses, or clinical support staff. Some initial investment in training healthcare professionals and staff on how to calculate, interpret, and act on the RAI may be necessary.

Use of the RAI may lead to increased monitoring, additional nursing assessments, or increased consultation for children identified as high risk. These downstream activities may incur additional costs, though they may also prevent costly complications through appropriate early intervention. Overall, the resource use and costs associated with the RAI are relatively low compared with the potential clinical benefits of identifying children at high risk for severe AKI and RRT.

Considerations for implementation

The RAI is most effectively applied early during hospitalization, particularly within the first 12–24 hours of admission or onset of critical illness. Clear identification of target populations (i.e., critically ill children) is important to avoid unnecessary application in people at low risk.

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Integration of the RAI into routine clinical workflows can enhance feasibility and consistency. Where available, embedding automated RAI calculation and alerts within the EHR may reduce healthcare professional burden and improve uptake. In settings without electronic automation, standardized paper or electronic checklists can be used with minimal additional resources. Education and training of physicians, nurses, and allied health professionals are essential to ensure correct calculation, interpretation, and appropriate clinical response to RAI results.

Institutions should define how RAI results will inform care pathways. For children identified as high risk, predefined kidney-protective strategies may include enhanced monitoring of urine output, kidney function and damage biomarkers, review and minimization of nephrotoxic medications, and optimization of fluid and hemodynamic management. The RAI should be used to support, not replace, clinical judgment, and healthcare professionals should remain attentive to evolving clinical changes that may warrant action despite a low RAI score.

Rationale

Given the value of early AKI risk stratification, the consistency of observational evidence supporting the predictive performance of the RAI, and the low risk of harm associated with its use, the Work Group suggests the use of the RAI in critically ill children at risk for AKI to assess the likelihood of severe AKI. The overall certainty of evidence is low, reflecting the predominance of observational studies and absence of outcome-driven interventional trials, supporting a Level 2 recommendation.

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CHAPTER 3. PREVENTION AND TREATMENT OF AKI

Numerous prevention and treatment strategies have been investigated for AKI. Given the central role of the kidneys in regulating fluid balance and BP, derangements in these parameters are closely associated with the development of AKI. Much of the evidence generated to prevent and mitigate AKI in acutely ill patients has focused on hemodynamic management strategies, including intravenous fluids and vasoactive/inotropic support, guided by clinical assessment (mental state, heart rate, respiratory rate, peripheral perfusion, capillary return, skin turgor, oedema), physiological and biochemical information (urine output, SCr, lactate concentration, biomarkers, and pH), and hemodynamic parameters (cardiac output, BP, central venous pressure, pulse pressure variation, stroke volume variation).

AKI is not a uniform entity. While many aspects of care are applicable to prevention and management of all causes of AKI, some strategies are specific to particular etiologies. Distinct forms of AKI include AKI that occurs in the perioperative setting, hepatorenal syndrome, tumor lysis syndrome, rhabdomyolysis, and pregnancy-associated AKI.

Current evidence for AKI prevention and management has primarily been shaped by research on hospital-acquired AKI in high-resource settings. This knowledge often does not fully address the unique risk factors, diagnostic challenges, socioeconomic aspects, and resource limitations in low- and middle-resource settings. Addressing community-acquired AKI requires public health-oriented strategies including community education, improved access to clean water, early recognition and referral systems, and scalable, low-cost treatment options alongside individualized clinical management.

3.1 Fluid management

Recommendation 3.1.1: We recommend using crystalloids rather than colloids (albumin, gelatin, or starches) as initial management for intravascular volume expansion in children and adults at risk of or with AKI or AKD (*1B*).

This recommendation puts high value on evidence from large RCTs consistently demonstrating superiority of crystalloids over artificial colloids and equivalence with natural colloids (e.g., albumin) for preventing AKI, need for RRT, and mortality. It also places value on the lower cost of crystalloids compared with colloids. It places a lower value on the potentially greater, but short-lived hemodynamic effects of colloids. It does not apply to people with hemorrhagic shock, in whom blood products are appropriate for resuscitation.

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Key information

Balance of benefits and harms

This recommendation aligns with the KDIGO 2012 AKI guideline, which provided an extensive review of this subject. A network meta-analysis of 49 RCTs (including 40,910 critically ill adults) included comparisons of crystalloids versus high- and low-molecular weight hydroxyethyl starch (HES).[306] The study found a significantly lower risk of any stage AKI (OR: 0.55; 95% CI: 0.34–0.88) and RRT (OR: 0.51; 95% CI 0.27–0.93) with crystalloid fluids versus high molecular weight HES (Supplementary Table S39), but no significant difference versus low molecular weight HES (OR for AKI: 0.91; 95% CI: 0.73–1.21; OR for RRT: 0.74; 95% CI 0.52–1.15; Supplementary Table S40). However, the likelihood of mortality was lower among people treated with crystalloids than either high molecular weight HES (OR: 0.76; 95% CI: 0.58–0.99) or low molecular weight HES (OR: 0.88; 95% CI: 0.78–0.99). A systematic review and meta-analysis of 3 RCTs comparing gelatin-containing plasma expanders versus crystalloids or albumin in a total of 212 patients showed no significant difference in AKI.[307]

Key studies in the field published subsequent to the KDIGO 2012 AKI guideline include the Crystalloid versus Hydroxyethyl Starch Trial (CHEST),[308] and the Scandinavian Starch for Severe Sepsis/Septic Shock (6S) trial; these trials focus on lower molecular weight HES.[309] The CHEST trial demonstrated no difference in mortality but an increase in RRT in those treated with 6% HES (7.0% vs. 5.8%, p=0.04).[308] The 6S trial in adults with sepsis demonstrated that resuscitation with 6% HES increased mortality (RR: 1.17; 95% CI: 1.01–1.36; p=0.03) as well as development of AKI requiring RRT (RR: 1.35; 95% CI: 1.01–1.80, p=0.04) with a trend towards an increase in major bleeding events compared to resuscitation with Ringer's acetate.[309]

In a network meta-analysis of 58 RCTs (including 26,351 participants), various fluids, including albumin, were compared in adults with sepsis, surgical, trauma and traumatic brain injury. No significant differences in risks of death, AKI, or composite adverse events were observed between crystalloids and either iso-oncotic or hyperoncotic albumin in separate analyses of adults with sepsis, surgery, or trauma (Supplementary Table S41).[310, 311] However, few RCTs directly compared crystalloids with albumin and effect estimates were generally imprecise. For example, among adults undergoing surgery receiving either crystalloids or iso-oncotic albumin, there were imprecise estimates for likelihood of mortality (OR: 0.99; 95% CI: 0.48–2.03; 5 RCTs with direct comparisons, including 180 participants[312-316]) or AKI (OR 1.19; 95% CI: 0.27–5.15; no direct comparisons).[310] A systematic review that included more recent RCTs of adults undergoing major surgery had similar imprecise estimates (OR for mortality: 0.84; 95% CI: 0.19–3.70: OR for AKI: 1.01; 95% CI: 0.41–2.42).[311]

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These results are consistent with those of a Cochrane systematic review of 69 RCTs published between 2013 and 2018 (involving 30,020 participants) comparing colloids with crystalloids for resuscitation.[317] Across 20 trials (13,047 participants), albumin or fresh frozen plasma showed no difference in mortality compared to crystalloids (RR: 0.98; 95% CI: 0.92–1.06), and there was no difference in the need for RRT (RR: 1.11; 95% CI: 0.96–1.27). However, use of HES was associated with a 30% increased risk for RRT (RR: 1.30; 95% CI: 1.14–1.48; 9 studies, 8527 participants).

There are fewer studies investigating the effects of fluid types in children. A meta-analysis of 3 RCTs (including 924 children) showed no evidence that the choice of gelatin versus albumin or crystalloids affected the risk of death (RR: 1.21; 95% CI: 0.94–1.57) or any stage of AKI (RR: 0.36; 95% CI: 0.04–3.23; Supplementary Table S42).[307] These findings are consistent with the results of a systematic review and meta-analysis of 12 clinical trials including 3526 children less than 18 years of age admitted to the pediatric emergency and ICU with severe infection and shock requiring fluid resuscitation.[318] The study found no significant difference in the mortality rate in children with either sepsis or malaria between those who received crystalloids versus colloids (RR: 0.94; 95% CI: 0.76–1.17; 5 RCTs). Only one small RCT of 60 participants evaluated the risk of AKI, comparing colloids versus crystalloids, and found a highly imprecise, nonsignificant difference (RR: 0.36; 95% CI: 0.04–3.23).[319]

Certainty of evidence

There is moderate certainty evidence that in critically ill adults, high molecular weight HES increases the risk of death and risk of AKI requiring RRT with low certainty of evidence of an increase in incident AKI compared with crystalloids (buffered or saline 0.9%).[306, 320] The certainty of evidence was downgraded for methodological limitations and further downgraded for AKI due to sparseness of data.

Similarly, there is moderate certainty evidence low molecular weight HES increases the risk of death in critically ill patients; however, there is low certainty of evidence of no increased risk of AKI or AKI requiring RRT compared with crystalloids (buffered or saline 0.9%).[306, 309] The certainty of evidence was downgraded for methodological limitations and further downgraded for AKI and RRT due to imprecision.

In various populations of adults at increased risk for AKI, including those undergoing surgery, having sepsis, or having experienced trauma, there is very low certainty of evidence of no difference in death or incident AKI between balanced crystalloids and either iso-oncotic or hyperoncotic albumin (based primarily on a network meta-analysis), with no evidence regarding harms.[310, 311] The certainty of evidence was downgraded because of

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imprecise estimates, sparse data, and indirectness due to lack of studies that directly compared balanced crystalloids and albumin.

In critically ill children with hypervolemia, there is moderate certainty of evidence of no difference in risk of death between gelatin and albumin or crystalloids. The certainty of evidence was downgraded due to imprecision; however, there was very low certainty regarding the relative effect on risk of AKI due to a highly imprecise estimate from a single study.[307] With higher certainty of evidence for death than AKI, we assessed the overall certainty of evidence to be moderate.

Values and preferences

This recommendation places a high value on minimizing the risk of AKI or AKD, and on the use of interventions with the most favorable balance of benefits to risks. The Work Group judged that, for most people, the potential kidney and systemic harms associated with the use of colloids, especially synthetic starches, outweigh any uncertain or modest benefits related to intravascular volume expansion.

The recommendation also reflects a preference for crystalloids because they are widely available, familiar to healthcare professionals, less costly, and supported by evidence suggesting comparable or superior safety with respect to kidney outcomes. The Work Group recognized that some patients or healthcare professionals may value potential short-term hemodynamic effects of colloids or have specific clinical circumstances where albumin is considered. However, given the low certainty of evidence for benefit and the consistent signal for harm with certain colloids, most well-informed patients would likely prefer crystalloids as initial therapy to reduce kidney-related risks. Specific people (e.g., Jehovah's witnesses) may object to receiving albumin because it is derived from human blood.

Resource use and costs

The Work Group considered resource utilization and costs to be important factors in formulating this recommendation. Crystalloids are inexpensive, widely available across a broad range of healthcare settings, and do not require specialized storage or administration, making them feasible for use in both high- and low-resource settings. Albumin is significantly more expensive than crystalloids and requires human plasma for production. Artificial colloids, including gelatins and starches, are more expensive than crystalloids and are not available everywhere.

Use of some colloids is also associated with increased downstream resource utilization due to higher rates of RRT, which may further increase overall healthcare costs. Avoiding these colloids as initial therapy may therefore reduce both direct acquisition costs and indirect costs related to complications and prolonged hospitalization. Overall, routine use

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of more expensive colloid solutions does not represent a cost-effective use of healthcare resources.

Considerations for implementation

Implementation of this recommendation requires ensuring that crystalloids are readily available and prioritized as the default fluids for initial intravascular volume expansion. Institutional protocols, order sets, and clinical pathways should reflect crystalloids as first-line therapy, with clear guidance on fluid selection and correct use. Education of clinicians, nurses, and pharmacists is important to reinforce the rationale for avoiding colloids in this population and to promote consistent practice across care settings. The Work Group acknowledges that albumin may still be considered in specific clinical circumstances or disease states based on healthcare professional judgment or other guideline recommendations;[252, 321, 322] such use should be clearly justified and documented. Protocols and pathways should indicate that synthetic starches should be avoided.

Rationale

Shock and intravascular volume depletion (including bleeding) can trigger AKI. Consequently, intravascular volume expansion is needed in these settings. The choice of fluid depends on the type of fluid lost. Blood products are the fluid of choice for resuscitation of hemorrhagic shock. In the absence of hemorrhagic shock, the Work Group judged that crystalloids offer a more favorable risk–benefit balance for initial fluid management in people at risk of or with AKI or AKD compared to colloids. Although the certainty of evidence is low (Grade C), the consistency of findings demonstrating lack of benefit and potential harm, coupled with considerations of safety, availability, and cost, supports a Level 1 recommendation in favor of crystalloids as first-line therapy. This recommendation is consistent with the Surviving Sepsis Campaign International Guidelines recommendation for using crystalloids rather than albumin for initial fluid resuscitation in children and adults with septic shock or sepsis-associated organ dysfunction.[323]

Recommendation 3.1.2: We recommend using buffered crystalloids instead of 0.9% saline for volume expansion in the absence of traumatic brain injury in children and adults at risk of or with AKI or AKD (*1B*).

This recommendation puts a high value on the reduced AKI incidence, severity, and treatment with RRT with buffered crystalloids compared to 0.9% saline. It places a lower value on their accessibility and potentially higher costs. This recommendation does not apply to people with traumatic brain injury, in whom 0.9% saline may be preferred due to concerns about the impact on intracranial pressure with solutions of lower serum osmolality, or choice of fluids for prevention of tumor lysis, heme-pigment or contrast-associated AKI. Buffered crystalloids may reduce the risk of hyperchloremia and metabolic acidosis compared with

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0.9% saline, which is relevant in people at risk of or with AKI or AKD. The choice of buffered crystalloid may be influenced by availability and costs.

Key information

Balance of benefits and harms

Chloride-rich solutions like 0.9% saline may cause renal vasoconstriction and ischemia resulting in AKI.[324, 325] A meta-analysis of 21 RCTs (including 36387 adults) showed lower mortality with the use of buffered crystalloids compared with 0.9% saline, with a RR of 0.96 (95% CI: 0.92–1.00; Supplementary Table S43). In 12 trials including 29,241 adults, the incidence of AKI was lower with buffered crystalloids versus 0.9% saline (RR: 0.93; 95% CI: 0.87–0.99) as was RRT use (RR: 0.92; 95% CI: 0.84–1.01), although the latter was not statistically significant.[326-330]

The study that reinvigorated interest in buffered solution was an open-label, single center sequential period study of chloride-restricted solutions (Hartmann's solution, Plasmalyte-148, and low chloride albumin) versus chloride-rich fluids that demonstrated a reduction in Stage 2 or 3 AKI, including reduced need for RRT, with the use of chloride-restricted solutions.[331] The subsequent 0.9% Saline vs Plasma-Lyte 148 (PL-148) for ICU fluid Therapy (SPLIT) trial did not demonstrate significant effects of buffered solutions on AKI incidence , RRT, or mortality.[332] However, the indications for fluid therapy were not specified, 71% of subjects were enrolled postoperatively and had already received fluids in a nonrandomized manner during surgery, and the overall exposure to study fluids was relatively low (a median of 2 liters) during ICU stay.

Two large, pragmatic, multiple crossover, single-center cluster clinical trials subsequently demonstrated benefit of buffered fluids on MAKE at 30 days ($MAKE_{30}$) among critically ill adults in the ICU as well as adults admitted to non-ICU settings from the emergency department.[333, 334] In the Isotonic Solutions and Major Adverse Renal Events Trial (SMART),[334] the rate of $MAKE_{30}$ was 14.3% in the buffered crystalloids arm compared to 15.4% in the 0.9% saline arm among critically ill adults (OR: 0.90; 95% CI: 0.82–0.99; p=0.04). In the Saline against Lactated Ringer's or Plasma-Lyte in the Emergency Department (SALT-ED) trial,[333] the overall $MAKE_{30}$ incidence was lower than observed in the critically ill population, but a statistically significant difference in this outcome favoring buffered crystalloids was still observed (OR: 0.82; 95% CI: 0.70–0.95; P=0.01).

Individual subsequent patient-level RCTs have been unable to confirm these findings. Neither the Plasma-Lyte 148 versus Saline (PLUS) trial[335] nor the Balanced Solutions in Intensive Care Study (BASICS)[336] demonstrated reductions in 90-day mortality or improvement in kidney outcomes with buffered crystalloids. Nonetheless, multiple meta-

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analyses based on the totality of evidence that have since been published have demonstrated a modest effect of buffered crystalloids on AKI and mortality.[337]

Beyond the effects of clinical outcomes of AKI, RRT, and mortality, the hyperchloremic metabolic acidosis that develops with the use of 0.9% saline has been associated with increased resource utilization. In a retrospective propensity matched analysis of participants undergoing major abdominal surgery in the U.S., not only was the use of Plasmalyte-148 associated with lower rates of mortality and AKI compared to participants who received 0.9% saline, but also with fewer arterial blood gas and lactate measurements.[338]

Of note, buffered solutions are slightly hypotonic compared to 0.9% saline. Three trials reported outcomes of buffered crystalloids versus 0.9% saline among 1896 adults with traumatic brain injury at baseline. In this population, randomization to buffered crystalloids increased mortality (RR: 1.26; 95% CI: 0.98–1.60).[337] This finding suggests that the benefits and harms of buffered crystalloids differ in those with traumatic brain injury who are at risk for cerebral edema with solutions of lower osmolarity. In light of this finding, the recommendation excludes people with traumatic brain injury, in whom individualized fluid management based on consideration of potential benefits and harms was deemed more appropriate.

A meta-analyses of 4 RCTs of critically ill children with and without severe sepsis or septic shock (896 participants) showed that administration of buffered fluids versus 0.9% saline was associated with a reduced need for RRT (OR: 0.53; 95% CI: 0.34–0.84) but no difference in mortality (OR: 0.92; 95% CU: 0.69–1.23), incident AKI (OR: 0.89; 95% CI: 0.57–1.41), or $MAKE_{30}$ (OR: 0.47; 95% CI: 0.08–2.81; Supplementary Table S44).[339-342]

A different systematic review included 12 RCTs involving 3526 children with severe infection and septic shock of whom 96% of participants were from low- and middle-resource settings.[318] The use of buffered crystalloids compared to 0.9% saline was associated with a reduced risk of AKI (RR: 0.67; 95% CI: 0.53–0.85) and hyperchloremia (RR: 0.69; 95% CI: 0.58–0.82), with no difference in mortality (RR: 0.99; 95% CI: 0.81–1.22) but with shorter duration of hospital stay (mean difference [MD]: −0.66 days).[339-341, 343-352]

Certainty of evidence

There is moderate certainty of evidence that in critically ill adults without traumatic brain injury, compared with 0.9% saline, buffered crystalloids reduce the risk of death, development of AKI, and treatment with RRT, with no evidence of harms.[326-330, 334, 336, 347, 348, 353-355] The certainty of evidence was downgraded due to some methodological limitations across studies. Effect estimates for mortality and AKI in adults were precise, but there was imprecision in adults for the estimate of the effect on RRT.

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There is moderate certainty of evidence that in critically ill children, buffered fluids reduce the risk of RRT, but there is no evidence of reduction in other AKI-related outcomes or death, compared with 0.9% saline, with low or very low certainty of evidence.[339-341, 343-352] There was no evidence regarding harms. The certainty of evidence was downgraded due to methodological limitations across studies and due to imprecision for estimates of effect on mortality and AKI in children. Given the higher certainty of evidence regarding RRT than AKI, the overall certainty of evidence was graded as moderate.

Values and preferences

From the point of view of patients, the use of one crystalloid type versus another feels identical. Most well-informed patients would prefer an option where the totality of evidence suggests it may have a small effect on lowering mortality, reduces the incidence of AKI, and avoids metabolic complications such as hyperchloremia and metabolic acidosis, which may precipitate the need for RRT.

The Work Group recognized that healthcare professionals and patients may value the simplicity, availability, and perceived safety of 0.9% saline, and that individual clinical circumstances; such as traumatic brain injury, specific electrolyte abnormalities, or local resource constraints; may influence fluid choice. Therefore, it is logical to support the administration of buffered solutions, except for situations where their administration could be harmful (e.g., in people at risk of or with traumatic brain injury or cerebral edema) or they remain relatively unstudied (e.g., tumor lysis syndrome prophylaxis), or when the administration of such fluids might delay care (e.g. during shock or crush injury, when a delay in care may be detrimental).

Resource use and costs

Some buffered crystalloids such as lactate Ringer's solution or Hartmann's solution are widely available and have costs that are similar to 0.9% saline in many jurisdictions, though costs up to 1.1–2 times higher than 0.9% saline have been described in low- and middle-resource settings.[356] However, Plasma-Lyte is less widely accessible, and its price varies between countries and can be substantially higher than 0.9% saline. While the magnitude of benefit of buffered solutions in terms of RRT, MAKE, or mortality is low, over 30 million patients receive intravenous fluids every year, making fluid therapy a fundamental component of acute care.[357] From a population health perspective, the benefit of even small effects on clinical outcomes such as RRT and mortality is significant and supportive of cost utility. Further, use of buffered crystalloids may reduce the incidence of hyperchloremic metabolic acidosis and related complications, which can prompt additional laboratory testing, therapeutic interventions, and prolonged hospitalization, further supporting cost-effectiveness.

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The Work Group acknowledged that the cost and availability of buffered crystalloids vary across regions, and 0.9% saline may be the only readily accessible isotonic fluid in some low-resource settings. In such contexts, the recommendation should not impede timely volume resuscitation. Overall, given the modest incremental cost and the potential to improve outcomes and reduce downstream resource utilization, the Work Group judged buffered crystalloids to represent a reasonable and potentially cost-effective option for volume expansion.

Considerations for implementation

Implementation of this recommendation requires that buffered crystalloids be readily available and incorporated as the default option for volume expansion in most acutely ill patients. Saline (0.9% saline) remains the most widely available intravenous fluid globally, including in low resource settings, due to established supply chains and lower production costs. Buffered solutions are less consistently available. Lactate Ringer's is more commonly stocked than other buffered solutions, though its availability can still be limited by procurement policies, local manufacturing capacity, and supply chain constraints. Plasma-Lyte and similar solutions are less available, often restricted to tertiary care centers or urban hospitals. Implementation of this recommendation is expected to require changes to manufacturer incentives and institutional procurement of intravenous fluid solutions to supply buffered solutions at scale.[358] Policy interventions and procurement strategies may be needed to ensure equitable access.

Institutional policies, order sets, and clinical pathways should be updated to reflect buffered crystalloids as first-line fluids, with clear indications for when 0.9% saline remains appropriate, including traumatic brain injury or specific clinical scenarios, for instance as carrier substance for certain medications. Education of healthcare professionals is important to promote understanding of the physiologic differences between buffered crystalloids and 0.9% saline and the rationale for preferential use in this population.

Rationale

Fluid therapy is a key component of the prevention and management of AKI and AKD, and the composition of administered fluids may influence kidney outcomes and mortality. Saline (0.9% saline) contains a supraphysiologic chloride concentration, which can lead to hyperchloremia, metabolic acidosis, and renal vasoconstriction, potentially reducing kidney perfusion and contributing to AKI.

Buffered crystalloids more closely approximate the electrolyte composition of plasma and include metabolizable anions that reduce the chloride load and help maintain acid–base balance. RCTs and meta-analyses have demonstrated lower rates of AKI outcomes and

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mortality in adults and lower incidence of RRT and AKI in children with use of buffered crystalloids compared with 0.9% saline. Overall, outside of specific situations (fluid administration in traumatic brain injury, and volume expansion for prevention of tumor lysis, heme pigment- and contrast-associated AKI), buffered crystalloids offer better kidney and patient outcomes than 0.9% saline for children and adults, though availability may be limited and cost implications are relatively greater for these solutions in low- and middle-resource settings.

The Work Group judged that the balance of benefits and harms favors buffered crystalloids over 0.9% saline for volume expansion in most people with or at risk of AKI or AKD. This recommendation excludes people with traumatic brain injury, in whom maintenance of higher serum osmolality and avoidance of potential increases in intracranial pressure are prioritized, and patients with tumor lysis syndrome (Practice Point 3.7) or rhabdomyolysis (Practice Point 3.8.1) where buffered crystalloids are understudied, and those receiving intravenous crystalloids for prevention of contrast-associated AKI (Recommendation 4.9.2.1).

Recommendation 3.1.3: For children and adults with AKI or AKD who have severe metabolic acidosis with acidemia (pH <7.20), we suggest the use of intravenous bicarbonate over RRT unless there is another urgent indication for RRT (*2C*).

Intravenous sodium bicarbonate can correct metabolic acidosis, attenuate hyperkalemia, and potentially stabilize hemodynamics, thereby decreasing the application of RRT. However, RRT should be initiated promptly if there is another urgent indication, such as refractory hyperkalemia, severe volume overload, or symptomatic uremia. Healthcare professionals should monitor for potential complications of bicarbonate therapy, including volume expansion, hypernatremia, and paradoxical intracellular acidosis.

Key information

Balance of benefits and harms

Metabolic acidosis with severe acidemia is regarded as an indication for RRT unless corrected medically. Sodium bicarbonate therapy is typically administered as either an isotonic infusion or a hypertonic 4.2% or 8.4% infusion. However, these solutions may be associated with complications related to volume overload and shifts in systemic pH. Potential benefits with the use of sodium bicarbonate therapy in this setting are improvement in pH and hyperkalemia as well as a better response to vasoactive medications.

A meta-analysis of RCTs comparing intravenous bicarbonate versus usual care in children and adults with metabolic acidosis with and without AKI showed a lower incidence of RRT (4 trials, 1071 participants; RR: 0.69; 95% CI: 0.60–0.80) but no significant

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differences in mortality (4 trials, 1140 participants; RR: 0.88; 95% CI: 0.71–1.07), length of ICU or hospital stay, or incidence of $MAKE_{90}$ (Supplementary Table S45).[359-365]

A pivotal study in this field was the Sodium bicarbonate therapy for patients with severe metabolic acidemia in the ICU (BICAR-ICU) trial, a 26-center, open-label, RCT.[360] Adults admitted to the ICU with severe acidosis (defined as pH ≤7.20 with a $paCO_2$ ≤45 mm Hg and serum bicarbonate concentration ≤20 mmol/l) and with a Sequential Organ Failure Assessment (SOFA) score ≥4 or an arterial lactate ≥2 mmol/l were randomized to receive treatment with 4.2% sodium bicarbonate infusion aiming to keep arterial pH ≥7.30 or placebo. The primary outcome was a composite of death by day 28 and at least one organ failure at day 7. Although there was no overall difference with regards to the primary outcome, in a prespecified analysis focused on participants with Stage 2 or 3 AKI (as defined by the AKIN criteria), survival at day 28 was higher in the bicarbonate arm compared to control (54%; 95% CI: 45%–65% vs. 37%; 95% CI: 28%–48%, p=0·0283). The use of RRT was lower in participants with AKI treated with sodium bicarbonate (51% vs. 73%, p=0.002).

Subsequently, the second RCT of sodium bicarbonate in the ICU (BICARICU-2) evaluated whether intravenous 4.2% sodium bicarbonate therapy targeting a serum pH ≥7.30 compared with no intravenous sodium bicarbonate therapy could improve outcomes in critically ill adults with severe acidemia and Stage 2 or 3 AKI.[361] In this trial, intravenous sodium bicarbonate therapy had no effect on 90-day mortality (62.1% vs. 61.7%; absolute difference: 0.4; 95% CI: −7.2 to 8.0). However, a secondary endpoint of RRT use was reduced in adults receiving intravenous sodium bicarbonate (35% vs. 50%; absolute difference: –15.5; 95% CI: –23.1 to –7.8). Among participants who received RRT, the time to initiation was longer in those allocated to intravenous sodium bicarbonate therapy compared with controls (30.9 hours vs. 15.5 hours). The findings of this trial thus suggest that intravenous sodium bicarbonate can delay or avoid the use of RRT in critically ill adults with severe acidemia and moderate to severe AKI, with no greater risk of adverse events. One limitation of the trial was that it was an open-label trial.

In children, the evidence for bicarbonate in AKI is limited. In an open label RCT, the efficacy and safety of bicarbonate infusion to correct bicarbonate deficit was compared to rehydration therapy in 50 children in India with acute diarrhea and severe dehydration with severe non-anion gap metabolic acidemia.[365] The group treated with additional bicarbonate infusion experienced a shorter time to resolution of metabolic acidemia, greater acidemia resolution by 8 hours and 16 hours, less vasoactive use, fewer adverse events, and shorter duration of mechanical ventilation.

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Certainty of evidence

There is high certainty of evidence that in children and adults who are critically ill with acidosis, intravenous bicarbonate reduces the risk of RRT. There is low to moderate certainty of evidence of no effect on mortality, other kidney outcomes, or harms.[359-365] The evidence base included 6 studies in adults and one in children,[365] with consistent findings across studies of children and adults. The certainty of evidence for outcomes other than RRT was downgraded for methodological limitations, imprecision, and/or sparseness of data. Given the higher certainty of evidence of an effect regarding RRT than other outcomes, the overall certainty of evidence was graded as high.

Values and preferences

This recommendation places a high value on avoiding the risks and resource intensity associated with RRT, including vascular access complications, hemodynamic instability, and exposure to extracorporeal therapies, particularly in settings where RRT may be limited or delayed. It places a lower value on the potential for incomplete or transient correction of acidemia with intravenous bicarbonate therapy. Patient and healthcare professional preferences regarding invasiveness of therapy, availability of RRT, and anticipated reversibility of acidosis may influence decision-making. Patients and healthcare professionals may reasonably choose RRT earlier when there is limited response to bicarbonate therapy or other urgent indications for RRT are present.

Resource use and costs

Intravenous sodium bicarbonate is widely available, relatively inexpensive, and can be administered in most acute care settings without specialized equipment or personnel. In contrast, RRT requires substantial resources, including equipment, trained staff, vascular access, and monitoring, and may be limited by availability, particularly in resource-constrained settings. Use of bicarbonate therapy in appropriate patients may reduce or delay the need for RRT and its associated costs. However, bicarbonate administration requires monitoring for treatment response and may not obviate the need for RRT in people with persistent or worsening acidosis or other indications. Local resource availability and institutional expertise may influence decision-making.

Considerations for implementation

Bicarbonate is typically administered intravenously. When administered as an isotonic infusion, bicarbonate is often given in a 5% dextrose solution and can lead to significant hyperglycemia. More concentrated bicarbonate solutions (4.2% and 8.4%) are significantly hypertonic and can result in hypernatremia. Bicarbonate can lower ionized calcium and potassium levels due to changes in systemic pH. If sodium bicarbonate therapy is administered very rapidly (e.g., as a “push” dose) in people with severe respiratory failure, the inability to ventilate off newly generated carbon dioxide may result in a transient

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worsening of acidemia.[366] Bicarbonate is incompatible with a number of intravenous medications and often requires a dedicated lumen for infusion, which may be a challenge in a person with limited intravenous access. In case of extravasation, hypertonic bicarbonate can cause severe skin necrosis due to its chemical properties.

Rationale

Severe metabolic acidosis is a common complication of severe AKI and may contribute to hemodynamic instability, impaired myocardial contractility, and increased respiratory workload. Intravenous sodium bicarbonate can rapidly increase systemic pH and buffer excess hydrogen ions, thereby mitigating the physiological consequences of acidemia. Bicarbonate may increase responsiveness to vasoactive drugs in people with shock.

RCTs suggest that bicarbonate therapy can correct acidemia and reduce the need for RRT in people with severe metabolic acidosis and moderate-to-severe AKI, likely by attenuating both acidemia and hyperkalemia as both can trigger the decision to start RRT. However, effects on mortality and other patient-important outcomes remain uncertain. RRT can correct acid–base disturbances but is invasive, resource-intensive, and associated with risks, including vascular access complications and hemodynamic instability. In the absence of other urgent indications for RRT, an initial trial of intravenous bicarbonate may stabilize patients and allow time for kidney recovery.

Practice Point 3.1.1: Offer oral rehydration to children and adults at risk of or with AKI or AKD being managed in settings where volume expansion with intravenous fluid administration is not possible or practical.

Given the significant morbidity and mortality associated with AKI in settings where intravenous fluid administration is not feasible, oral hydration can be a practical, low-cost, and life-saving intervention for volume resuscitation and should be offered to children and adults at risk of or with AKI, provided there are no contraindications to oral intake. The World Health Organization (WHO) explicitly recommends oral rehydration therapy as the first-line treatment for mild-to-moderate dehydration and recognizes it as a critical, life-saving intervention in community and healthcare settings without intravenous access (https://www.who.int/news-room/fact-sheets/detail/diarrhoeal-disease).

Recommendation 3.1.4: For adults undergoing elective major abdominal surgery, we recommend a liberal intravenous fluid management strategy, aiming for a positive fluid balance gain of 1–2 kg at 24 hours after surgery, over a restrictive strategy (net zero fluid balance) (*1B*).

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This recommendation puts a high value on the RCT evidence demonstrating the superiority of a liberal intravenous fluid regimen to achieve normovolemia compared with a restrictive fluid management regimen for preventing AKI and the need for RRT among adults receiving elective major abdominal surgery. It places a higher value on the benefits of reducing the incidence of AKI and RRT over the potential harm of increasing the incidence of pulmonary edema with a liberal fluid strategy. It acknowledges that additional fluid administration can be needed for resuscitation of unstable patients to achieve hemodynamic stability, euvolemia, and tissue perfusion in the perioperative period.

Key information

Balance of benefits and harms

Observational studies have shown that both excessive and insufficient perioperative fluid administration are associated with increased length of hospital stay and morbidity, including AKI.[367-370]

The REstrictive Versus LIbEral Fluid Therapy in Major Abdominal Surgery (RELIEF) trial was a large, pragmatic, multicenter RCT of almost 3000 participants undergoing major elective abdominal surgery that compared a restrictive with a liberal intravenous fluid approach.[371] Participants assigned to the restrictive fluid group had a body weight increase of 0.3 kg versus 1.6 kg in the liberal fluid group in the first 24 hours after surgery. The primary outcome, disability-free survival at 1 year, was similar in both groups. However, the occurrence of AKI (8.6% vs. 5.0%; RR: 1.72; 95% CI: 1.30–2.27) and the need for RRT (0.9% vs. 0.3%; RR: 3.24; 95% CI: 1.06–9.92) were significantly higher in participants randomized to restrictive fluid management, while the incidence of pulmonary edema (1.4% vs. 2.2%) was non-significantly higher in the group that received fluids more liberally. The increase in the absolute risk of RRT (7 excess events per 1000) was numerically similar to the reduction in pulmonary edema (8 fewer events per 1000) with a restrictive versus liberal fluid approach. Compared with pulmonary edema, which is typically reversible and amenable to prompt medical management, incident RRT represents a substantially more severe and consequential complication, associated with higher morbidity, prolonged hospitalization, and potential long-term kidney disease. Seven other much smaller trials mostly support the findings of the RELIEF trial, except that RRT was less common across the other trials, yielding a less precise estimate of the effect of fluid restriction on need for RRT (summary RR: 1.96; 95% CI: 0.73–5.25; Supplementary Table S46).[371-375]

In light of these relative benefits and harms, providing liberal intravenous fluids to achieve an euvolemia and a mildly positive fluid balance at the end of surgery can be considered preferable to restricting intravenous fluid administration with the aim of zero balance within the first 24 hours of major elective abdominal surgery. This recommendation applies to stable adults going for elective abdominal surgeries. Fluid administration may need

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to be adjusted for adults with hypotension or hypovolemia in the perioperative period based on volume status and fluid losses and according to dynamic assessments of fluid responsiveness where available. The majority of evidence comparing liberal versus restrictive fluid management was generated in patients undergoing major elective non-abdominal surgery.[376]

Certainty of evidence

There is moderate certainty of evidence that, in adults undergoing major elective abdominal surgery, a liberal fluid strategy decreases the risk of AKI, Stage 3 AKI, and possibly RRT, with no difference in mortality or fluid-related adverse events.[371-375, 377-379] The certainty of evidence was downgraded primarily for sparseness of studies supporting the conclusions, because summary estimates largely recapitulated a single large trial, or imprecision of effect estimates.

Values and preferences

Intravenous fluids are universally administered during and after major surgery. The significant decrease in risk of AKI provides a reason for patients to prefer a liberal fluid strategy because patients typically view RRT as highly undesirable because of the additional burden and experience with this treatment and its association with need for long-term RRT, prolonged hospitalization, and risk of CKD. Although pulmonary complications related to fluid overload (e.g., pulmonary edema) are also clinically important, these are often amenable to effective medical management, and patients may prefer to accept a modestly higher risk of transient and mild (about 1–2 liters) volume overload over an increased risk of AKI or requirement for RRT, which carry greater immediate and long-term burdens. Accordingly, many patients and healthcare professionals will prioritize strategies that minimize the risk of AKI, including a slightly higher fluid balance perioperatively, provided that fluid administration remains judicious and balanced against potential harms of fluid excess.

Resource use and costs

A liberal fluid strategy does not markedly change the costs directly related to fluid administration itself, as the additional resource use associated with delivering a liberal fluid strategy is minimal. On the other hand, for every 167 people treated, one person will avoid the costs and resources associated with RRT. A strategy that minimizes avoidable AKI has the potential to reduce hospital length of stay, critical care use, dialysis resources, and post-discharge health care utilization that has been associated with AKI, thereby favorably influencing overall cost and resource burden.

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Considerations for implementation

Implementation of a liberal perioperative fluid strategy requires clear institutional protocols that define target fluid goals and emphasize avoidance of both under-resuscitation and excessive fluid loading. Education of anesthesia, surgical, and postoperative care teams is important to ensure shared understanding of the evidence from the RELIEF trial, particularly the higher risk of AKI observed with restrictive strategies despite no improvement in disability-free survival. Healthcare professional training should acknowledge that fluid administration should be accompanied by regular reassessment using clinical and hemodynamic parameters (e.g., BP, urine output, lactate, and dynamic measures of fluid responsiveness where available) rather than rigid adherence to fixed volumes.

Integration with existing enhanced recovery after surgery (ERAS) pathways should be undertaken thoughtfully, as many ERAS programs emphasize restrictive fluid approaches. The RELIEF trial was a pragmatic trial that allowed healthcare professionals to provide boluses or adjust administration of intravenous crystalloids, colloids, bloods products, and use of vasopressors as deemed clinically appropriate in response to hypotension and hypovolemia, thus individual patient factors should be considered when applying this recommendation. Of note, the RELIEF trial included patients undergoing elective major abdominal surgery. Whether there is a role for liberal perioperative fluid management in major non-abdominal surgery is uncertain.

Rationale

Perioperative fluid management seeks to maintain euvolemia and adequate tissue perfusion and organ function while minimizing the risks of both fluid overload and under-resuscitation. The RELIEF trial; a large, pragmatic RCT in adults undergoing major abdominal surgery; directly compared a restrictive versus a liberal intravenous fluid strategy. Although the trial did not demonstrate a difference in the primary outcome of disability-free survival at 1 year, it showed that the restrictive strategy was associated with a higher incidence of AKI compared with a liberal fluid approach. This finding suggests that too stringent fluid restriction may compromise renal perfusion and increase the risk of AKI, including RRT.

Given that AKI is linked to increased morbidity, longer hospital stays, and greater health care resource use, the evidence supports a moderate liberal fluid strategy targeting a modest positive fluid balance to reduce AKI and need for RRT without incurring excessive harm from fluid excess. The recommendation reflects a balance between ensuring adequate intravascular volume to support organ perfusion and avoiding unnecessary fluid overload, with appreciation of patient-centered outcomes and safety.

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3.2 Hemodynamic management

Practice Point 3.2.1: Use hemodynamic monitoring strategies for adults at risk of and with AKI to assess adequate organ perfusion and oxygen delivery, which will be context-sensitive and resource availability dependent.

Hemodynamic monitoring is intended to ensure maintenance of adequate intravascular volume, cardiac output, and tissue oxygenation.[380] Autoregulatory mechanisms regulate kidney blood flow within a broad range of pressures to preserve a stable GFR. Preexisting conditions including CKD and hypertension, and events including sepsis, major surgery and AKI itself, may disrupt kidney autoregulation, contributing to ischemia and AKI.[381] Recognition and correction of inadequate organ perfusion are central to AKI prevention and mitigation in vulnerable people. Hemodynamic monitoring provides a framework to guide timely and individualized interventions aimed at maintaining sufficient kidney blood flow and systemic oxygen delivery while avoiding harm from over-resuscitation. Large observational studies have shown that the degree and duration of hypotension during major surgery and critical illness are associated with AKI and major adverse kidney events.[382, 383] The Intraoperative Norepinephrine to Control Arterial Pressure (INPRESS) study reported a significantly lower risk of postoperative organ dysfunction, including AKI in adults who received an individualized BP management strategy compared to standard BP management during major surgery.[380] However, subsequent RCTs did not confirm these findings.[384-386]

The choice and intensity of hemodynamic monitoring should be tailored to the clinical context, severity of illness, and available resources. In all settings, careful clinical assessment, including trends in BP, heart rate, urine output, mental status, capillary refill, and peripheral perfusion are fundamental. Where available, adjunctive tools for continuous BP monitoring, pulse oximetry, serum lactate measurement, and bedside ultrasound can enhance assessment of intravascular volume status, cardiac function, and organ perfusion. In higher-acuity environments, advanced (invasive or minimally invasive) hemodynamic monitoring (e.g., arterial catheters, central venous pressure monitoring, or advanced cardiac output monitoring) may be considered to support complex decision-making.

Establishing advanced hemodynamic monitoring is relatively common in high resource settings.[387] Invasive devices like pulmonary artery catheters are associated with potential complications, including thrombosis, bleeding, and infection, which may negatively affect patients' outcomes and increase costs and resource utilization. Increasingly, less invasive tools like echocardiography are used to determine cardiac output and monitor haemodynamics.[387]

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The additional costs for using advanced hemodynamic monitoring need to be considered against the benefits of optimizing a patient's hemodynamics, including greater resource use and longer stay in the ICU and hospital. Therefore, the choice of hemodynamic monitoring strategy should balance goals to optimize perfusion while minimizing iatrogenic injury. In resource-limited settings, reliance on structured clinical assessment and basic monitoring can still support effective hemodynamic management and AKI risk reduction.

Children have unique cardiovascular physiology and limited autoregulatory capacity, making them especially vulnerable to hypotension and fluctuations in cardiac output. Kidney autoregulation is immature in neonates and can be easily disrupted by critical illness, congenital heart disease, or sepsis, leading to impaired kidney blood flow even when systemic pressures appear adequate. There are no RCTs evaluating advanced hemodynamic monitoring for AKI prevention in pediatric populations. The Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates study (AWAKEN) identified an association between hemodynamic instability, including hypotension and vasopressor use, and increased risk of AKI in neonates.[35] Similarly, in children undergoing cardiac surgery, multiple studies have demonstrated that low perfusion pressure, high vasoactive-inotropic scores, and prolonged cardiopulmonary bypass times are independently associated with increased AKI incidence.[388-391]

Practice Point 3.2.2: Use vasoactive medications in conjunction with fluids in children and adults with hypotension not responsive to initial fluid administration and who are at risk of or have AKI.

The maintenance of adequate BP and oxygen delivery to organs is a key aspect of resuscitation and hemodynamic support. In many people with sepsis, bleeding, or other forms of shock, an adequate mean arterial pressure (MAP) cannot be maintained with fluid resuscitation alone, and vasoactive medications are necessary. Hypotension is a strong risk factor for development and progression of AKI, and hemodynamic optimization is a key component of the kidney-protection strategy.

The costs of the most common vasoactive medications are relatively low, but some vasopressors have higher costs. Further, not all vasoactive medications are available in all regions. While vasoactive medications are typically administered through central venous catheters, the peripheral administration of a vasopressor, like norepinephrine, for a limited period (usually up to 6 hours) and at a low dose can be both expedient and safe using explicit protocols.[392]

Repeated assessments of fluid status, hemodynamics, and fluid responsiveness are needed to guide management and to identify the time point when further fluid administration

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is no longer beneficial and/or vasopressor support is needed (alone or in combination with fluids).

Recommendation 3.2.1: We suggest a mean arterial pressure (MAP) of >65 mm Hg as a target to guide fluid and vasopressor administration in critically ill adults at high risk of or with AKI (*2C*).

Practice Point 3.2.3: Higher or lower MAP targets may be appropriate for individual critically ill adults, for instance to maintain renal perfusion in patients with chronic hypertension and to avoid adverse effects of excessive vasopressor therapy in patients with chronic hypotension.

This recommendation puts a high value on targeting adequate perfusion pressure to maintain organ function. The suggested MAP target of >65 mm Hg should be interpreted as a general guide rather than a fixed threshold and may require individualization based on baseline BP. Higher MAP targets may be necessary to maintain adequate renal perfusion, while in others, lower targets may be acceptable to avoid excessive vasopressor exposure or fluid administration. The MAP should be considered alongside other indicators of perfusion and kidney function and integrated within a multimodal hemodynamic management strategy.

Key information

Balance of benefits and harms

The potential benefits of targeting a MAP >65 mm Hg include improved organ perfusion, including kidney blood flow, maintenance of glomerular filtration, prevention of progression of AKI, and positively modifying the trajectory of AKI. A MAP-based target provides a practical and widely applicable framework to guide fluid resuscitation and vasopressor therapy, particularly in dynamic critical care environments. The potential harms relate primarily to the interventions used to achieve the MAP target rather than the target itself. Excessive fluid administration may contribute to complications of fluid overload. Increased vasopressor exposure may be associated with arrhythmias, peripheral and mesenteric ischemia, increased myocardial oxygen demand, and decreased cardiac output. In some subgroups of people, including those with chronic hypertension or advanced vascular disease, a MAP of >65 mm Hg may be insufficient, while in others, higher targets may increase the risk of treatment-related adverse effects without clear additional benefit. Targeting a specific MAP without considering other indices of perfusion or adverse effects has led to ambiguous results from trials comparing MAP targets, so that MAP threshold should not be considered in isolation.

Meta-analysis of 2 RCTs comparing higher versus lower MAP targets in critically ill participants with chronic hypertension showed that targeting a higher MAP was associated

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with a significantly lower risk of AKI (RR: 0.75; 95% CI: 0.59–0.95) and need for RRT (RR: 0.83; 95% CI: 0.71–0.97) but also a higher risk of mortality (RR: 1.19; 95% CI: 1.01–1.40) when compared with a lower MAP target (Supplementary Table S47).[393, 394] In these trials, MAP targets were 80–85 mm Hg versus 65–70 mm Hg (with mean achieved MAPs of 85 mm Hg vs. 75 mm Hg),[395] 75–80 mm Hg versus 60–65 mm Hg (with mean achieved MAPs of 79 mm Hg vs. 70 mm Hg),[393] and usual care versus 60–65 mm Hg (with mean achieved MAPs of 73 mm Hg vs. 68 mm Hg).[394]

A single RCT explored the role of higher versus lower MAP targets in adults with chronic hypertension undergoing cardiac surgery and showed that targeting a MAP ≥70 mmHg during cardiopulmonary bypass was associated with a higher risk of postoperative AKI (RR: 4.59; 95% CI: 1.02–20.71) and uncertain effect on mortality (RR: 9.09; 95% CI: 0.50–166.7; Supplementary Table S48).[396] In one trial investigating participants with chronic hypertension undergoing non-cardiac surgery, there was no statistically significant difference in the incidence of AKI, need for RRT or mortality between participants with a higher (≥80 mm Hg) or lower (≥65 mm Hg) MAP target (Supplementary Table S49).[397] Across 3 RCTs that individualized MAP targets in participants, there were no significant benefits (or harms) of targeting higher MAP targets, but in one study that targeted individualized MAP goals within 10% of the patient's individual reference value during major non-cardiac surgery, there was a lower incidence of AKI (adjusted RR: 0.70; 95% CI: 0.52–0.92) and lower risk of needing RRT (adjusted RR: 0.85; 95% CI: 0.29–2.48) with no difference in risk of mortality (Supplementary Table S50).[380, 384, 386]

A limitation of these RCTs in critically ill participants is that they evaluated different MAP thresholds during the stabilization phase but not at the initial phase of resuscitation. Further, blood flow of different organs depends on organ-specific perfusion pressure which is determined by the difference between inflow and outflow pressure and autoregulatory processes. The MAP value at which organ blood flow is directly dependent on perfusion pressure varies across organs.[398] These considerations and evaluation of all vital organs need to be considered when setting MAP targets in clinical practice. The target MAP to prevent AKI in people who are not critically ill or not scheduled to have major surgery is not known.

When vasopressor support is indicated, norepinephrine remains the most frequently used medication. However, norepinephrine is not available worldwide. There are a variety of vasopressors available in clinical practice, with differing mechanisms of actions and potential benefits and harms. Furthermore, these vasopressors differ in how they impact kidney function (Table 21).

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Table 21 | Vasopressors for management of adults with or at risk of AKI*

Drug	Characteristics	Rationale for use in AKI	Evidence from RCTs
Norepinephrine	• α1, α2, β1, β2 and β3 receptor agonist	• Better renal perfusion in septic shock compared to other catecholamines	• No significant difference in RRT in people with septic shock between norepinephrine versus dopamine (SOAP II study[399])
Vasopressin	• Endogenous hormone • V1 and V2 receptor agonist	• Possibly preferential constriction of efferent glomerular arteriole resulting in increased GFR • Augmentation of diuresis • Regulation of urine osmolality resulting in change in urine volume	• Lower rate of progression from AKI RIFLE Risk to RIFLE Failure or Loss or RRT in people with septic shock randomized to vasopressin compared to norepinephrine (VASST trial[400]) • No difference in kidney failure-free days but higher urine volumes and lower rate of RRT with early addition of vasopressin to noradrenaline in septic shock (VANISH trial[401]) • Less kidney injury in people with vasoplegic shock after cardiac surgery with vasopressin compared to norepinephrine (VANCS trial[402]).
Terlipressin	• Synthetic vasopressin analogue	• Greater selectivity for the V1-receptor and longer half-life than vasopressin	• Significantly lower rise in serum creatinine but no difference in RRT with continuous infusion of low-dose terlipressin as 1st line vasopressor in septic shock (TERLIVAP trial[403]).
Phenylephrine	• Pure α1 agonist	• Possible beneficial effects on hepato-splanchnic perfusion in septic shock	• No difference in urine output and creatinine clearance between phenylephrine and norepinephrine for septic shock[404]
Angiotensin II	• Endogenous hormone • Part of renin-angiotensin-aldosterone-axis	• Stronger vasoconstrictive effect on glomerular efferent arteriolar tone than afferent arteriole	• Faster liberation from RRT with angiotensin compared to placebo in people with refractory vasoplegic shock on noradrenaline (sub-analysis of ATHOS-3 study[405])
Selepressin	• Analog of vasopressin, agonist of V1A receptor	• Vasopressin agonist with less non-vascular adverse effects than vasopressin	• No difference in urine output compared to placebo in people with septic shock treated with norepinephrine[406]

*There is no compelling rationale to use either epinephrine or dopamine in people with or at risk for AKI to prevent or manage AKI, though these agents may be used clinically to keep MAP at target. Reproduced from Busse *et al*.[407] Abbreviations: AKI, acute kidney injury; ATHOS-3, Angiotensin for the Treatment

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of High Output Shock phase IIB-III trial GFR, glomerular filtration rate; RIFLE, Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease classification of acute kidney injury; RRT, renal replacement therapy; SOAP II, Sepsis Occurrence in Acutely Ill Patients II trial (Comparison of Dopamine and Norepinephrine in the Treatment of Shock); TERLIVAP, Continuous terlipressin versus vasopressin infusion in septic shock trial; VANCS, Vasopressin versus Norepinephrine in Patients with Vasoplegic Shock after Cardiac Surgery trial; VANISH, Vasopressin vs Norepinephrine as Initial Therapy in Septic Shock trial; VASST, Vasopressin and Septic Shock Trial

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Certainty of evidence

For critically ill adults with chronic hypertension, there is moderate certainty of evidence that treating adults with high MAP goals (target MAP ≥70 mm Hg) results in lower risk of the need for RRT, but with a higher risk of mortality. There is low certainty of evidence of a lower risk of AKI.[393-395] The certainty of evidence was downgraded for some methodological limitations of the RCTs and, for AKI, sparse data (1 large study).[393-395] Given the conflicting direction of effect between mortality and AKI-related outcomes, the overall certainty of evidence was graded as low.

Based on a single RCT, for adults with chronic hypertension undergoing cardiac surgery, there is low certainty of evidence that treating people with high MAP goals (target MAP ≥70 mm Hg) results in higher risk of AKI, but no evidence of an effect on mortality or need for RRT.[396] The certainty of evidence was downgraded for sparse data and imprecise data.[396]

For adults with chronic hypertension undergoing non-cardiac surgery, there is very low certainty suggesting no difference in mortality or AKI outcomes between those treated with high (target MAP ≥80 mm Hg) and lower MAP goals.[397, 408] The certainty of evidence was downgraded for sparse data (single study for most outcomes), imprecision, and inconsistency.[397, 408]

Also for adults with chronic hypertension undergoing non-cardiac surgery, there is low certainty of evidence that individualized MAP goals (which varied across RCTs) do not affect mortality, AKI outcomes, or serious adverse events.[380, 384, 386] The certainty of evidence was downgraded for methodological limitations of the trials, inconsistency (pertaining to effect on AKI), and imprecision.[380, 384, 386]

Values and preferences

Maintenance of an adequate MAP is a fundamental component of supportive care that aligns with healthcare professional and patient priorities to preserve organ function during critical illness. A MAP threshold of >65 mm Hg is familiar to healthcare professionals, facilitates timely decision-making, and supports standardized care while allowing for bedside clinical judgment, evaluation of response, and individualization. Targeting a higher or lower MAP will lead to administration of more or fewer vasoactive medications and fluid. A lower value was placed on strict adherence to a single BP target in all people, acknowledging heterogeneity in baseline BP, comorbid conditions, and tolerance of fluids or vasopressors. Patients and healthcare professionals may differ in their preferences regarding the balance between avoiding hypotension and minimizing exposure to fluids and vasopressors, particularly when these therapies carry risks of harm.

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The Work Group also considered patient values related to overall goals of care, comfort, and avoidance of treatment-related complications. In some clinical contexts, particularly in patients with limited physiological reserve or advanced illness, patients may prioritize minimizing invasive interventions over aggressive BP targets.

Resource use and costs

Higher MAP targets will necessitate greater use of vasoactive medications (higher doses and longer duration) and likely administration of more fluid. The incremental resource use associated with this target is expected to be low, as it does not mandate additional diagnostic testing or equipment beyond standard care.

The Work Group acknowledged that in some settings, particularly resource-limited environments, access to continuous BP monitoring or vasoactive medications may be constrained. In such contexts, healthcare professionals may rely on intermittent monitoring and clinical signs of perfusion to approximate MAP targets. Despite these limitations, the recommended MAP threshold remains relevant as a guiding principle for hemodynamic management.

Considerations for implementation

It is important to note that in trials targeting a particular MAP, protocol adherence was variable. For instance, in the 65 Trial (RCT comparing MAP target >65 mm Hg vs. permissive hypotension with a MAP target of 60–65 mm Hg in critically ill patients aged ≥65), the actual delivered MAP differed significantly from the prescribed MAP goals (i.e., the MAP achieved in the permissive hypotension arm [target MAP 60–65] was 66.7 mm Hg).[394] These results reflect the challenge to achieve and maintain exact MAP targets, even in the setting of a clinical trial. Other challenges exist when people need vasopressor support but also medications that may potentially lower the MAP, for instance, beta-blockers for coronary artery disease. In these cases, an individualized risk assessment is needed to guide specific management.

Achieving the MAP target requires judicious use of intravenous fluids and vasopressors, guided by ongoing assessment of volume status, cardiac function, and overall tissue perfusion. Fluids should be administered cautiously to avoid volume overload, especially in people with established AKI or limited cardiac reserve. Vasopressor therapy should be titrated to the lowest effective dose to achieve the target MAP, with close monitoring for adverse effects. MAP should not be used in isolation but rather as part of a multimodal assessment of end-organ perfusion. Regular reassessment is essential, particularly during changes in clinical condition or therapeutic interventions. The international, multicenter ANDROMEDA-SHOCK-2 trial randomized 1467 adults with early septic shock and showed that individualized hemodynamic management to tailor fluids,

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vasopressors, and inotropes was superior to usual care, in particular with regards to duration of vital support, including duration of RRT.[409]

Rationale

Observational studies and RCTs in critically ill populations have consistently demonstrated associations between the duration and severity of hypotension and adverse kidney outcomes, including higher rates of AKI, need for RRT, and mortality.[410, 411] Targeting a MAP >65 mm Hg to guide fluid administration and vasopressor support in critically ill adults is recommended based on RCTs that have not shown benefit of routinely targeting higher MAP levels for kidney outcomes. Higher targets are associated with increased exposure to fluids and vasopressors. Accordingly, a MAP of >65 mm Hg represents a balance between avoiding renal hypoperfusion and limiting treatment-related harms.

A MAP target is readily measurable, familiar to healthcare professionals, and can be implemented across diverse critical care settings. Importantly, MAP should be interpreted in the context of individual patient characteristics, as patients with chronic hypertension or altered vascular autoregulation may require higher perfusion pressures to maintain adequate kidney blood flow.

The Work Group judged that targeting a MAP of >65 mm Hg is supported by moderate-certainty evidence, strong biological plausibility, and extensive clinical experience. Given the variability in patient response and the potential risks associated with aggressive hemodynamic support, the recommendation is Level 2 and emphasizes individualized application within a multimodal strategy for kidney protection.

Recommendation 3.2.2: We recommend against using low-dose dopamine for kidney protection in children or adults at risk of or with AKI or AKD (*1A*).

Low-dose dopamine has been used to improve renal perfusion based on the physiological principle that dopaminergic receptor stimulation increases kidney blood flow, which in turn increases GFR. However, there is consistent evidence that low-dose dopamine does not prevent AKI, improve kidney recovery, or reduce the need for RRT and may cause harm. Dopamine may still be indicated for other hemodynamic purposes according to standard critical care practice, but such use should not be expected to confer kidney benefit and should not be used with the intent of preventing or treating AKI.

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Key information

Balance of benefits and harms

No benefit has been demonstrated with dopamine at a low dose in terms of any clinical or kidney outcome. This evidence was previously reviewed in the KDIGO 2012 AKI guideline, and this recommendation has not changed. Subsequent trials of low-dose dopamine have examined dopamine in people with acute heart failure and abnormal kidney function (e.g., ROSE[412]) and have not shown an improvement in decongestion.

Evidence from well-performed clinical studies to support the use of low-dose dopamine for children with or at risk for AKI is lacking. A systematic review analyzed 7 studies evaluating its effects on kidney function and 13 studies on urine output, all conducted in neonatal or pediatric ICUs.[413] The investigators reported no evidence that low-dose dopamine improved kidney function or increased urine volume in children.

Certainty of evidence

Based on evidence summarized in the KDIGO 2012 AKI guideline, there is high certainty of evidence that low-dose dopamine neither affects risk of AKI in critically ill patients nor affects clinical outcomes for people with AKI, with some evidence of harms including tachyarrhythmias and myocardial ischemia.[414-416]

Values and preferences

Because the evidence shows that dopamine is not effective, dopamine administration is associated with increased cost and exposure of patients to an unnecessary medication with the potential for serious adverse drug events, including tachycardia and arrhythmias, which patients and healthcare professionals prefer to avoid.

Resource use and costs

Dopamine is often administered via a central venous catheter. Patients may require admission to an ICU to receive such infusions. Thus, there are significant potential costs without benefits to the use of dopamine for kidney protection.

Considerations for implementation

This practice does not have evidence of efficacy and low-dose dopamine should not be part of protocols or order sets intended for kidney protection or treatment of AKI in both pediatric and adult populations. Education of healthcare professionals may be needed to address persistent misconceptions regarding low-dose dopamine and to reinforce the evidence demonstrating lack of benefit and potential harm.

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Rationale

The rationale for the use of dopamine is from experimental studies showing that dopaminergic receptors are present in the kidney and that their stimulation leads to increased blood flow. The inference has been that such an increase in blood flow would lead to an increase in GFR and thereby improve kidney function. However, clinical studies have not demonstrated beneficial effects on AKI or related clinical outcomes.

Recommendation 3.2.3: We recommend the use of a multicomponent kidney-protection strategy in adult surgical patients at high risk for AKI identified by clinical factors and biomarkers (Figure 9; *1B*).

Practice Point 3.2.4: In children and adults with established AKI or AKD, kidney-protection strategies should be considered.

This recommendation puts a high value on the RCT evidence demonstrating that the implementation of a multicomponent kidney-protection strategy in people at high risk for AKI reduced the incidence of moderate or severe AKI compared with standard care. A multicomponent kidney-protection strategy typically includes optimization of hemodynamics and volume status, avoidance or minimization of nephrotoxic exposures, appropriate glycemic control, judicious use of contrast agents, and close monitoring of kidney function. The specific components and intensity of the strategy may be individualized according to patient characteristics and resource availability. In settings where biomarker testing is not available, clinical risk assessments may be used to identify people at high risk. A risk-benefit assessment and resource utilization often needs to be considered.

Key information

Balance of benefits and harms

The KDIGO 2012 AKI guideline described a multicomponent kidney-protection strategy to prevent and manage AKI. The key components are optimization of volume status and perfusion pressure, discontinuation, and avoidance of nephrotoxic agents when possible, monitoring of SCr and urine output, use of alternatives to radiocontrast agents, maintenance of normoglycemia, and consideration of functional hemodynamic monitoring.

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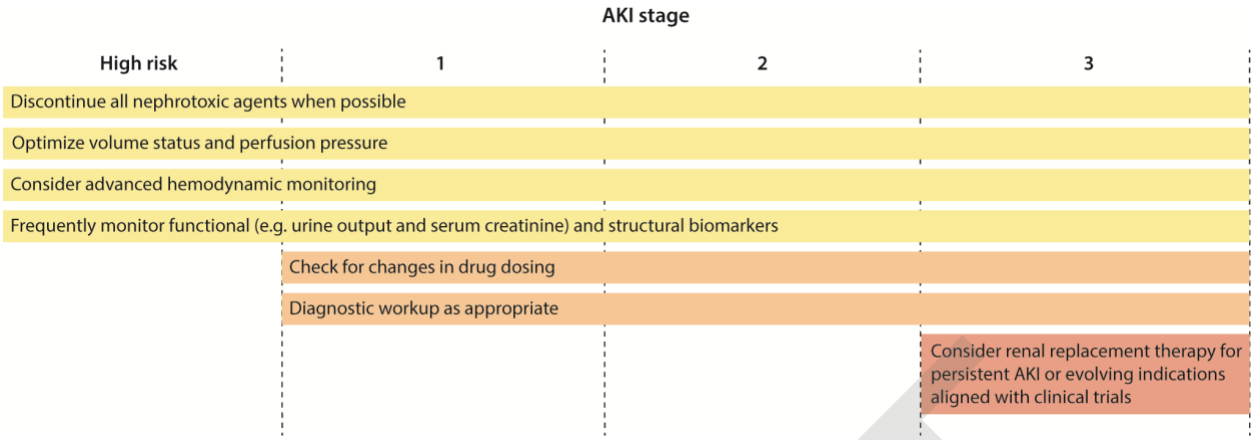
AKI stage
High risk
1
2
3
Discontinue all nephrotoxic agents when possible
Optimize volume status and perfusion pressure
Consider advanced hemodynamic monitoring
Frequently monitor functional (e.g. urine output and serum creatinine) and structural biomarkers
Check for changes in drug dosing
Diagnostic workup as appropriate
Consider renal replacement therapy for persistent AKI or evolving indications aligned with clinical trials

Figure 9 | Multicomponent kidney protection strategy for prevention and management of AKI. AKI, acute kidney injury

A meta-analysis of 5 RCTs including 1946 adult who were critically ill or undergoing major non-cardiac or cardiac surgery showed that the application of such a strategy was associated with a statistically significantly lower risk of Stage 2 or 3 AKI (OR: 0.67; 95% CI: 0.56–0.79) compared to usual care (Supplementary Table S51).[2, 4-6] The risk of $MAKE_{90}$ was also lower (OR: 0.80; 95% CI: 0.67–0.94) but there was no statistically significant difference in mortality or application of RRT.

One of the trials included was the "Prevention of Cardiac Surgery–Associated Acute Kidney Injury" (PrevAKI) trial, a single-center RCT that showed that implementation of the kidney-protection strategy in tubular stress biomarker-enriched patient population significantly decreased the occurrence of postoperative AKI compared with standard care in people at high risk undergoing cardiac surgery (absolute risk reduction: 16.6%; 95% CI: 5.5–27.9; P=0.004).[4] Similar results were seen in the subsequent multicenter PrevAKI trial.[2] Among 278 adults at high risk undergoing cardiac surgery, the occurrence of moderate and severe AKI was significantly lower in the intervention group as compared to the control group (14.0% vs. 23.9%; adjusted risk reduction 10.0%; 95% CI, 0.9–19.1; P=0.034). In exploratory multivariable analysis of participants with complete data on use of kidney-protection strategy measures (94% of participants), the prevention of hypotension and discontinuation of angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARBs) had the strongest association with the primary outcome.[417]

The "Biomarker-guided Intervention to Prevent Acute Kidney Injury After Major Surgery" (BigpAK) trial, another single center RCT that included participants at high risk undergoing major abdominal surgery, also demonstrated that early optimization of volume status and discontinuation of nephrotoxic medications in a biomarker-enriched patient population after surgery reduced the occurrence of Stage 2 or 3 AKI and shortened length of ICU and hospital stay.[5] Subsequently, the BigpAK-2 trial, a multicenter RCT including 1180 adults demonstrated that use of a kidney-protection strategy in participants at high risk for

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AKI identified by tubular stress biomarkers significantly reduced Stage 2 or stage 3 AKI after major noncardiovascular or cardiovascular surgery.[6]

Several trials have used tubular stress biomarkers to enrich selection of people at high risk of AKI into trials. In a meta-analysis of 4 studies including 775 participants, use of a kidney-protection strategy in people at high risk for AKI identified by elevated tubular stress biomarkers did not affect the incidence of any stage of AKI (OR: 0.70; 95% CI: 0.43–1.15; *P*=0.16) or Stage 1 AKI alone (OR: 1.07; 95% CI: 0.56–2.04; *P*=0.83) but was associated with a significantly lower incidence of Stage 2 or 3 AKI compared with standard care (OR: 0.55; 95% CI: 0.39–0.79; *P*=0.001).[418] A meta-analysis of 13 studies (including 5 RCTs) demonstrated a lower incidence of Stage 2 and 3 AKI, MAKE, and need for RRT among groups who received "AKI care bundles" (comprising early optimization of fluid status, maintenance of perfusion pressure, discontinuation of nephrotoxic agents).[419] Moreover, the incorporation of urine biomarkers within care bundles was associated with a lower risk of MAKE compared to care bundles without biomarkers.

Published trials have not reported any significant harm associated with the implementation of the kidney-protection strategy. However, some measures have potential adverse effects or complications. For instance, advanced hemodynamic monitoring and resuscitation might be associated with bleeding or initiation of catecholamines. Further, to maintain normoglycemia, the administration of higher amounts of insulin is often necessary which might increase the risk of hypoglycemia.

No RCTs have evaluated the full implementation of a kidney-protection strategy in pediatric populations but observational studies and quality improvement initiatives provide support for the core components. Nephrotoxin stewardship has been associated with reduced AKI incidence in hospitalized children; for example, the multicenter Nephrotoxic Injury Negated by Just-in-time Action (NINJA) program demonstrated a 23% relative risk reduction in AKI following targeted nephrotoxin surveillance and exposure reduction.[420] Pediatric quality improvement initiatives that incorporate fluid assessment, perfusion optimization, and kidney function monitoring have demonstrated potential benefit in high-risk settings.[421, 422]

Certainty of evidence

There is moderate certainty of evidence that in adults who are critically ill or undergoing major surgery, multicomponent kidney-protection strategies in biomarker-enriched patient populations reduce the risk of Stage 2 or 3 AKI and $MAKE_{90}$ with no evidence of an effect on all-cause mortality or need for RRT and no evidence of harm.[2, 4-6, 423, 424] The certainty of evidence was reduced for non-blinding of the RCTs.

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Values and preferences

All components of the KDIGO kidney-protection strategy are interventions that are fully integrated into routine modern clinical care and have known risk-benefit profiles. However, the kidney protection strategy is only implemented in a minority of patients at high risk for or with established AKI in daily practice. According to a systematic review, studies reported an AKI care bundle use in only 9.8% of eligible events.[419] Even with the aid of electronic recognition and interruptive alerts, an AKI bundle was completed within 24 hours in only 12.2% of AKI episodes.[425] The Work Group judged that most high-risk adults undergoing surgery, as well as their healthcare professionals, would prioritize kidney protection and avoidance of preventable harm, even when this requires additional monitoring, coordination of care, or modest increases in resource use. The recommendation emphasizes a multicomponent approach, recognizing that AKI in the surgical setting is typically multifactorial and more likely to be prevented by multiple different interventions. Combining clinical risk factors with biomarkers is valued for enrichment, improving risk stratification and enabling more targeted application of kidney-protective measures, thereby minimizing unnecessary interventions, and avoiding the increased complexity of care, implementation burden, costs, and the possibility of overtreatment in low-risk populations.

Resource use and costs

All components of the KDIGO kidney-protection strategy can be readily integrated into routine modern clinical care in high-resource settings but availability may be limited in low- and middle-resource settings. This strategy is expected to require additional upfront resource utilization, including costs related to biomarker testing, enhanced clinical monitoring, multidisciplinary coordination, and clinical decision support, which may be offset by the reduction in costs in managing AKI. Resource requirements may vary substantially across healthcare settings depending on the availability of laboratory infrastructure, perioperative care pathways, and staffing models. The inclusion of biomarkers to identify early phase AKI likely contributed to prevention of Stage 2 and 3 AKI, but these biomarkers are not routinely available in clinical practice in all healthcare systems and are associated with financial costs. Risk stratification using risk factors or prediction models may be used to target prevention strategies to high-risk populations in settings where biomarkers are not available. This can likewise help optimize resource allocation by focusing delivery of kidney-protection strategies on people most likely to benefit, thereby limiting resource use and costs of unnecessary testing or interventions in those at low risk. However, these strategies, including biomarker measurement, also increase the complexity of patient care.

Considerations for implementation

The individual components of the KDIGO kidney-protection strategy are part of modern medical care. However, it has been shown that they are not consistently applied in routine clinical practice.[426] Even in the context of a clinical trial, the adherence to the kidney-

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protection strategy in the intervention group is reduced.[418] Effective implementation may be facilitated by multidisciplinary collaboration among surgery, anesthesiology, nephrology, critical care, nursing, and pharmacy teams. Clear delineation of roles and responsibilities is important to ensure timely risk identification, consistent application of interventions, and appropriate monitoring. Incorporation of standardized order sets, checklists, or care bundles may improve adherence and reduce practice variation. Systematic clinical audits can help with monitoring adherence to kidney protection care bundles, identify barriers to bedside application, and facilitate data-driven improvements in patient outcomes. Use of clinical decision support tools within electronic health records may aid implementation by automating risk stratification, prompting appropriate interventions, and reducing reliance on individual healthcare professional recall.

Rationale

The implementation of a multicomponent kidney-protection strategy in surgical and critically ill adults at high risk for AKI is recommended based on a series of RCTs showing that their application reduced the incidence of moderate or severe AKI without an increased risk of complications or harm. Multicomponent kidney-protection strategies address the complex pathophysiology of surgical AKI by combining complementary interventions across the perioperative period, such as optimization of volume status and hemodynamics, avoidance or minimization of nephrotoxic exposures, drug stewardship, glycemic control, and enhanced monitoring of kidney function.[2, 4-6]

Kidney stress biomarkers have been used to identify people at high risk who are most likely to benefit from intervention for inclusion in many of the RCTs. However, their use requires access to specialized assays and timely laboratory processing. In many low-resource, rural, or non-tertiary care settings, such infrastructure is unavailable, and turnaround times may not support real-time decision-making. Excessive reliance on biomarkers in these settings could therefore delay risk identification or preclude implementation of kidney-protection strategies altogether.

The Work Group judged that early identification of people at high risk using readily available clinical information is preferable to delayed or absent risk assessment, particularly when the recommended interventions are low risk and broadly kidney protective. Use of clinical risk factors or predictive models enables equitable implementation of multicomponent kidney-protection strategies across diverse healthcare systems and reduces the risk of excluding people in resource-limited settings from preventive care.

The strength of this recommendation reflects the consistency of benefit observed with multicomponent approaches, the biological plausibility of targeting multiple injury pathways, and the substantial clinical consequences of AKI. Although the overall certainty of evidence

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is moderate due to limitation in study design and uncertain effects on important clinical outcomes, the Work Group judged that the anticipated benefits of reducing moderate-to-severe AKI in high-risk adults undergoing surgery outweigh the potential harms, supporting a Level 1 recommendation.

3.3 Use of diuretics

Recommendation 3.3.1: We suggest use of diuretics in the management of clinically significant volume overload of children and adults with or at risk of AKI or AKD (*2B*).

This recommendation puts a high value on the available physiological and clinical trial data that show that diuretics are effective at achieving volume removal and that, in situations where there is clinically relevant fluid accumulation, diuretics are both logical and desirable. Despite a theoretical potential kidney-protective benefit with loop diuretics, there is no evidence at present that diuretics reduce the incidence or severity of AKI, as articulated in the KDIGO 2012 guideline. If target volume removal can be achieved, they may prevent the need for RRT.

Key information

Balance of benefits and harms

Diuretics can induce fluid removal in most people unless they have anuric kidney failure. Potential benefits of an initial diuretic trial include improved fluid balance, relief of congestion-related symptoms, and avoidance or delay of RRT in selected people who are diuretic responsive. Side effects of diuretics include electrolyte disorders, metabolic alkalosis, ototoxicity (particularly with high doses of loop diuretics), and the potential for volume depletion and hypotension if prescribed without re-evaluation of volume status.

A Cochrane review assessed the effects of diuretics on the prevention (53 trials, 8078 participants) and treatment (11 trials, 1793 participants) of AKI.[427] For AKI prevention, diuretic use reduced the application of RRT (RR: 0.63; 95% CI: 0.43–0.91 in 32 studies with 4658 participants) and death (RR: 0.73; 95% CI: 0.59–0.92 in 33 studies with 6447 participants) and may reduce the risk of AKI (RR: 0.75; 95% CI: 0.61–0.92, I^2=77% in 38 studies with 5540 participants). When used for treatment of AKI, diuretics made little to no difference in the use of RRT or death and increased the risk of adverse events including hypotension (RR: 1.99; 95% CI: 1.16–3.41 in 2 studies with 720 participants) and arrhythmias (RR: 1.62; 95% CI: 1.12–2.33 in 6 studies with 1011 participants).

A recent pooled analysis of 10 RCTs in critically ill participants showed that protocolized fluid removal using diuretics compared to usual care after the acute phase of resuscitation resulted in little to no difference in mortality (RR: 0.90; 95% CI: 0.79–1.02) and no difference in the risk of developing AKI (RR: 0.78; 95% CI: 0.40–1.53) but the likelihood

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of receiving RRT was significantly lower with diuretic therapy (RR: 0.72; 95% CI: 0.55–0.96).[428]

The use of diuretics for the management of clinically significant volume overload in children with or at risk for AKI is supported by observational studies. Given the potential side effects including ototoxicity and nephrocalcinosis, loop diuretics should therefore be targeted to children with clear evidence of clinically significant volume overload.[429-431]

Certainty of evidence

The evidence supporting this recommendation was addressed by a Cochrane review.[427] The authors determined that the certainty of evidence was low for prevention of AKI (due to methodological concerns and inconsistency across trials), moderate for reduction of need for RRT and to reduce mortality (both due to methodological concerns), and low to reduce the need for chronic dialysis (due to being very imprecise), with low to very low certainty of evidence for serious adverse events. Based on this information, we determined that, overall, there is moderate certainty of evidence.

Values and preferences

This recommendation places a high value on alleviating the clinical consequences of volume overload, including respiratory compromise, impaired tissue oxygenation, and discomfort and the need for RRT. Patient preferences are driven by a desire to relieve symptoms, improve functional status, and reduce the risk of complications from volume overload, such as pulmonary edema and reduce RRT need since this is an invasive procedure. An initial trial of diuretics aligns with healthcare professional and patient preferences for a less invasive approach before escalation to RRT, particularly when there is residual kidney function and potential for diuretic responsiveness.

A lower value was placed on potential risks associated with diuretic therapy, such as electrolyte abnormalities or transient changes in kidney function, when diuretics are used judiciously and with appropriate monitoring of volume status.

Resource use and costs

Diuretics are widely available. The cost of diuretic therapy is low, and the resources associated with such therapy, including the need for electrolyte replacement, are relatively low. As their administration does not require specialized equipment and can typically be performed in both acute care and critical care environments, their use results in low incremental resource utilization. Potential cost savings may result from better management of volume overload, including reduced need for ventilatory support, shorter ICU or hospital length of stay, and avoided initiation of RRT.

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Considerations for implementation

Diuretics should be used with close monitoring of volume status, urine output, fluid balance, BP, and serum electrolytes, with prompt adjustment of therapy to avoid intravascular volume depletion, hypotension, or electrolyte disturbances. Diuretic choice, dosing, and route of administration should be individualized according to body weight, kidney function, prior diuretic exposure, and severity of volume overload. Weight-based dosing and careful monitoring are particularly important in children. Loop diuretics are most commonly used and can be administered orally or via the intravenous route. An inadequate diuretic response should prompt early reassessment of volume status and kidney function and consideration of combination therapy or alternative strategies, including escalation to RRT when clinically indicated. The combination of a loop and thiazide diuretic may augment diuresis and decrease the severity of loop diuretic-associated hypernatremia, which often requires significant free-water administration through the enteral or intravenous route, which can worsen volume overload.

Rationale

The removal of excess fluid is considered important because volume overload can contribute to organ dysfunction, including pulmonary dysfunction, increased need for mechanical ventilation, delayed wound healing, and AKI; if not corrected, fluid overload can cause patient discomfort and potentially become life-threatening. In both pediatric and adult populations, greater degrees of positive fluid balance have been consistently associated with increased severity of AKI and worse clinical outcomes.[432-434] Diuretics are effective for the management of volume overload, which is a key component of supportive care in people with or at risk of AKI or AKD. In people with residual kidney function, an initial trial of diuretics may facilitate achievement of a neutral or negative fluid balance and reduce complications related to congestion.

A Cochrane systematic review found that diuretics may reduce the incidence of AKI and probably reduce the need for RRT.[427] However, for the treatment of established AKI, diuretics did not meaningfully improve major kidney outcomes, including mortality or need for RRT, and were associated with potential harms such as hypotension. This supports closely monitored initial use of diuretics as a pragmatic and less invasive approach for volume management before escalation to RRT when there is potential for diuretic responsiveness.

This recommendation is supported by strong biological plausibility, consistent observational data linking volume overload with adverse outcomes, extensive clinical experience demonstrating the effectiveness of diuretics in relieving volume overload, moderate certainty of evidence that diuretics may reduce the need for RRT when used in early stages of AKI management, and other guidelines.[428]

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Practice Point 3.3.1: Intermittent boluses, rather than continuous infusions of loop diuretics, are appropriate as the initial diuretic management strategy in adults with or at risk of AKI or AKD.

The goal of diuretic use is to remove excess fluid effectively and safely without causing adverse events or prolonging the consequences of fluid overload. The majority of studies comparing bolus versus continuous infusion therapy have been performed in volume-overloaded participants with acute decompensated heart failure and have shown mixed results. A Cochrane meta-analysis of 7 RCTs concluded that there was little to no difference (benefit or harm) with continuous diuretic infusions compared to bolus dosing.[435]

Bolus dosing allows for rapid assessment of diuretic responsiveness, facilitates titration based on urine output and clinical response, and minimizes unnecessary prolonged exposure in people who are unlikely to respond. In the case of loop diuretics, the risk of ototoxicity is relatively low, though it is highest with high bolus doses, whilst continuous infusions may reduce peak serum concentrations. However, a continuous infusion requires the patient to be tethered to an infusion, typically via an infusion pump. Continuous infusions may be considered in selected people with demonstrated diuretic responsiveness who require sustained diuresis or in those with refractory volume overload to improve urine output or natriuresis, provided that close monitoring is ensured. Regardless of dosing strategy, lack of an adequate response should prompt reassessment of volume status and consideration of alternative therapies, including RRT when indicated.

Table 22 | Escalation pathway for diuretic therapy in AKI-related volume overload in adults

Step	Dose/administration	Monitoring/goal
Assessment	Furosemide 1.0 mg/kg (i.v. bolus). Use 1.5mg/kg if patient was previously on diuretics.	Goal: >200 ml urine output within 2 hours. If met, continue scheduled dosing until target fluid removal achieved.
Escalation	If Step 1 fails, double the dose (e.g., 160–200 mg i.v. bolus) every 6–12 hours.	Maximize bolus dose before switching to infusion. Max bolus: 200 mg.
Synergism	Add a thiazide-like diuretic (e.g., metolazone 5–10 mg p.o. or chlorothiazide 500 mg i.v.).	Administer 30–60 minutes before the loop diuretic to block distal sodium reabsorption.
Intensify	Switch to continuous i.v. infusion. Start at 5-10mg/hr.	Titrate up to 20 mg/hr (more effective for maintaining steady-state natriuresis)
Failure	Re-evaluate for RRT.	If net negative balance is not achieved despite max therapy or if K^+/pH are deranged.

AKI, acute kidney injury; i.v., intravenous; K, potassium; p.o., oral; RRT, renal replacement therapy

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Recommendation 3.3.2: We recommend initial use of diuretics in preference to extracorporeal fluid removal for adults at risk of or with AKI or AKD who have clinically significant volume overload in the absence of another indication for RRT (*1C*).

Diuretics and ultrafiltration are established strategies to remove excess fluid but have different risk-benefit profiles. While there is low certainty evidence of no difference in mortality, ultrafiltration is invasive, costly, and associated with risks, and, unless other indications are present, should be reserved for situations when initial attempts to manage volume overload with diuretics are unsuccessful.

Key information

Balance of benefits and harms

Fluid removal can be accomplished by 2 different methods: diuretics to augment fluid excretion by the kidneys or extracorporeal fluid removal. In both cases, delayed fluid removal prolongs the harmful effects of fluid overload and excessive fluid removal may lead to hypotension and worsening organ function, including AKI. The potential risks of either strategy must be balanced against the potential benefit of fluid removal and improvement of organ function. Benefits of diuretics include rapid initiation, ease of titration, and the ability to assess responsiveness over a short time frame with low treatment burden. Extracorporeal fluid removal is highly effective in achieving fluid removal but carries important risks, including intradialytic hypotension, myocardial ischemia, arrhythmias, and complications related to vascular access.

A meta-analysis of 9 RCTs comparing extracorporeal fluid removal versus diuretic therapy showed no difference in mortality and no evidence of benefit or harm regarding the risk of AKI (RR: 1.07; 95% CI: 0.79–1.45; Supplementary Table S52).[436] The majority of studies comparing these fluid removal strategies have focused on participants with acute decompensated heart failure with concurrent AKI. A pooled analysis of 4 RCTs conducted by an expert panel of the European Society of Intensive Care Medicine (ESICM) demonstrated no difference in mortality (RR: 1.13; 95% CI: 0.08–1.53) between fluid removal using ultrafiltration or RRT versus usual care, including the use of diuretics.[428] When evaluated, there was no significant difference in ventilator-free days, quality of life or risk of cognitive dysfunction between these strategies. There was also no significant difference in mortality in subanalyses of participants with fluid accumulation, respiratory failure, sepsis, or AKI.

Given the invasive nature of extracorporeal fluid removal compared with diuretics, the currently available evidence favors diuretic administration for fluid removal in adults at risk of or with AKI with clinically significant volume overload, provided kidney function is

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adequate to respond to diuretics, treatment response is closely monitored, and extracorporeal fluid removal can be initiated promptly when diuretics are ineffective or poorly tolerated.

Certainty of evidence

There is low certainty of evidence that, in adults with AKI and hypervolemia, there is no difference in mortality between diuretic use and application of RRT.[436] However, there is no trial evidence for AKI-specific outcomes or adverse events. The certainty of evidence was downgraded for methodological limitations of the trials and some imprecision.

Values and preferences

This recommendation acknowledges that, in general, people prefer noninvasive medical treatments over invasive interventions such as ultrafiltration (with central line placement and exposure to an extracorporeal circuit), unless there is clear evidence of benefit. Further, hemodynamic stability and preservation of residual kidney function are also valued, recognizing that extracorporeal fluid removal may expose people to risks of hypotension and ischemic complications. Overall, the recommendation reflects the judgment that most patients and healthcare professionals would prefer an initial, closely monitored trial of diuretics, with timely escalation to RRT only when clinically indicated and consistent with patient goals and preferences.

Resource use and costs

The use of an extracorporeal circuit for fluid removal is associated with greater resource use and costs, including the placement of vascular access appropriate for the extracorporeal circuit and the supplies needed for the extracorporeal circuit, including the device itself. In low resource settings, equipment for ultrafiltration may be inaccessible. Where the costs of ultrafiltration and RRT are paid out-of-pocket, use of extracorporeal fluid removal may put people at risk of rapid impoverishment.

Considerations for implementation

Both diuretics and extracorporeal fluid removal devices are well established therapies. They require good understanding of hemodynamics and fluid physiology and close monitoring. The necessary education is within the usual teaching in nephrology and critical care. Education for healthcare professionals should address appropriate use, monitoring, and reassessment to ensure consistent and safe implementation while allowing flexibility for individualized clinical judgment. Loop diuretics should be used most often, with attention to achieving an adequate initial dose to assess responsiveness. Intermittent bolus dosing is generally appropriate as the initial strategy, with escalation or combination diuretic therapy considered in selected patients. Identification of diuretic nonresponsiveness is essential. Clear criteria should be established for escalation to extracorporeal fluid removal, including

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persistent or worsening volume overload despite adequate diuretic therapy, intolerance to diuretics, or development of additional indications for RRT.

Rationale

The recommendation of diuretics over extracorporeal fluid removal measures is based on the lower costs, wider availability, and lower degree of invasiveness. Diuretics are effective for management of volume overload in adults who retain sufficient residual kidney function. An initial trial of diuretics may achieve meaningful fluid removal, improve pulmonary and tissue edema, and restore a more favorable fluid balance without exposing patients to the risks associated with extracorporeal therapies.

Extracorporeal fluid removal is highly effective in achieving fluid removal but is associated with important risks, including vascular access complications, bleeding, infection, and intradialytic hypotension, which may further compromise renal perfusion and contribute to kidney injury progression. In the absence of another clear indication for RRT, early use of extracorporeal fluid removal may therefore expose people to avoidable harms and increased treatment burden.

Direct comparative RCTs evaluating diuretics versus extracorporeal fluid removal for isolated volume overload in AKI are limited, resulting in low certainty of evidence. Nevertheless, the recommendation is supported by strong biological plausibility, consistent observational data linking volume overload to poor outcomes, and extensive clinical experience demonstrating that many patients can be effectively managed with diuretics alone. The Work Group judged that, for adults with clinically significant volume overload and no other indication for RRT, the anticipated benefits of an initial diuretic-based strategy outweigh the potential harms, provided that the response is closely monitored and escalation to extracorporeal fluid removal occurs promptly when diuretics are ineffective or poorly tolerated.

3.4 Glucose control

Practice Point 3.4.1: Insulin therapy targeting a plasma glucose level of 140–180 mg/dl (7.8–10 mmol/) is acceptable over more aggressive targets in critically ill children and adults with or at risk of AKI or AKD.

This is a change from the KDIGO 2012 guideline, which recommended a lower target glucose range of 110–149 mg/dl for prevention and management of AKI. The preponderance of current evidence is that intensive insulin therapy during acute illness does not improve survival.[435] In addition, no studies have focused on kidney outcomes as the primary outcome measure for such studies. A patient level meta-analysis of 38 trials including 29,537 participants found that intensive glucose control was not associated with a reduced mortality

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risk but increased the risk of severe hypoglycemia.[437] The risk of hypoglycemia is particularly high in people receiving RRT. There was no apparent benefit in any subgroup analyses. Furthermore, intensive glucose control requires frequent measurement of glucose levels and interferes with rest, in particular at night.

A secondary analysis of the Safe Pediatric Euglycemia After Cardiac Surgery (SPECS) trial investigated the impact of tight glycemic control on cardiac surgery-associated AKI in infants undergoing congenital heart surgery with cardiopulmonary bypass.[438] The study analyzed data from 799 children aged 0–36 months at 2 centers, comparing tight glucose control (target glucose 80–110 mg/dl) with standard glucose management. Cardiac surgery-associated AKI occurred in 36% of participants, predominantly Stage 2 or 3 (72%). Tight glucose control had no effect on reducing cardiac surgery-associated AKI or improving duration of mechanical ventilation, ICU or hospital stay, or mortality.[439]

3.5 Prevention of cardiac surgery-associated AKI

Recommendation 3.5.1: In adults without advanced CKD having cardiac surgery, we suggest that prophylactic intravenous amino acid administration can be used to prevent AKI (*2A*).

This recommendation puts a high value on the effect of intravenous amino acids on prevention of AKI and attenuation of its severity since AKI carries an increased cost of treatment and is a major risk factor for subsequent CKD and cardiovascular events. However, there is a lack of evidence for the benefit of amino acid infusion on long-term kidney function or important patient-centered outcomes. It is also uncertain whether the effect of amino acids on AKI outcomes is based on hyperfiltration leading to transient physiological changes in GFR versus prevention of structural kidney damage. Amino acid administration should be considered as an adjunct to, and not a replacement for, established perioperative kidney-protective measures such as optimization of hemodynamics, avoidance of nephrotoxins, and appropriate fluid management.

Key information

Balance of benefits and harms

Amino acid infusions have been studied for prevention of AKI in large numbers of adults receiving cardiac surgery, where they appear to be safe with no adverse drug reactions reported in comparison to placebo. Amino acids activate kidney functional reserve and increase kidney plasma blood flow, and in turn, GFR by approximately 40%. This effect may compensate for the decrease in GFR induced by cardiac surgery, resulting in prevention or attenuation of severity of AKI.

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In our meta-analysis of 6 RCTs including 4587 adults undergoing cardiac surgery, prophylactic administration of intravenous amino acids resulted in a lower incidence of postoperative AKI (RR: 0.80; 95% CI: 0.68–0.95) and significantly lower risk of Stage 3 AKI (RR: 0.52; 95% CI: 0.35–0.78) but without demonstration of significant difference in initiation of RRT (Supplementary Table S53).[440-444] No adverse drug reactions were reported across trials.

The majority of data comes from the multinational, double-blind Intravenous Amino Acid Therapy for Kidney Protection in Cardiac Surgery (PROTECTION) trial in 3511 adults undergoing cardiac surgery with cardiopulmonary bypass.[443] Adults with CKD G4 or G5 were excluded. Participants were randomized to receive an intravenous infusion of either balanced amino acids at a dose of 2 g/kg ideal body weight/day or placebo starting at operating room admission for up to 3 days. Postoperative AKI occurred in 474 participants (26.9%) in the amino acid group and in 555 participants (31.7%) in the placebo group (RR: 0.85; 95% CI: 0.77–0.94; *P*=0.002). Stage 3 AKI occurred in 29 participants (1.6%) and 52 participants (3.0%), respectively (RR: 0.56; 95% CI: 0.35–0.87). RRT was used in 24 participants (1.4%) in the amino acid group and in 33 participants (1.9%) in the placebo group (RR: 0.73; 95% CI: 0.43–1.22). There were no substantial differences between the groups in other secondary outcomes, including mortality or adverse events.

In a secondary analysis with focus on 812 participants with CKD,[445] intravenous amino acids significantly decreased the rate of AKI (43.1% vs. 50.3%; RR: 0.86; 95% CI: 0.74–0.99; *p*=0.041) with a median percentage increase in eGFR from baseline to postoperative day 3 of 12.7% versus 6.5% in the control group (*p*=0.002). The effect of amino acid infusion was similar across different eGFR-based CKD subgroups (30–39, 40–49, and 50–59 ml/min per 1.73 m^2). Finally, amino acid infusion decreased the occurrence of Stage 3 AKI (2.7% vs. 5.6%; RR: 0.48; 95% CI: 0.24–0.98; *p*=0.038).

A previous meta-analysis of perioperative use of amino acids assessed additional outcomes, including duration of mechanical ventilation, as well as ICU and hospital length of stay and mortality. Fifteen studies (14 RCTs and 1 prospective before-after study) reported at least one outcome of interest, with 6 studies (including 4084 participants) reporting the primary outcome.[446] AKI occurred in 24.7% of participants receiving amino acids versus 30.1% of controls (RR: 0.66; 95% CI: 0.47–0.94; I^2=50%; *p*=0.02). Moreover, consistent with these findings, amino acids increased the eGFR. While hospital length of stay was significantly shorter in participants treated with amino acids (MD: -1.02 days, 95% CI: -1.75 to -0.29, *p*=0.008), there was no significant difference in ICU length of stay; or mortality in ICU, hospital, or at longest follow-up.

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While there is evidence of short-term benefit with regard to AKI prevention based on KDIGO SCr criteria, there is a lack of evidence for the benefit of amino acid infusion for longer-term kidney function or clinical outcomes. In the PROTECTION trial, SCr concentration at 90 and 180 days after surgery were similar between the amino acid and placebo groups, although over half of participants were missing measurements at these timepoints. It is uncertain whether the effect of amino acids on AKI outcomes in these trials is based on hyperfiltration and transient physiological changes in GFR versus real prevention of kidney damage.

Certainty of evidence

There is high certainty of evidence that, in adults undergoing cardiac surgery, perioperative intravenous amino acids reduce the risk of any stage of AKI and Stage 3 AKI, but without evidence of a difference in RRT (due to imprecision) or benefits on long-term kidney function. No adverse reactions were reported across a large number of trials and participants.[440-444]

Values and preferences

This Level 2 recommendation places a high value on preventing postoperative AKI following cardiac surgery. Patients and healthcare professionals may prioritize interventions that reduce the risk of AKI and potential downstream adverse outcomes, even when the anticipated absolute risk reduction in AKI and length of hospital stay is modest. Further, prophylactic intravenous amino acid administration is relatively simple and short-term, with minimal burden to patients. However, this recommendation also acknowledges that no evidence of benefit of amino acids has been established for the need for RRT or long-term kidney function. Patients may reasonably differ in their willingness to receive an intervention with uncertain impact on outcomes they consider most important, especially in the context of complex cardiac surgery care.

Overall, the framing as a suggestion reflects the judgment that some healthcare professionals and patients, particularly those at high risk of AKI, may value a reduction in AKI or hospital stay. However, given the lack of demonstrated benefit on RRT, long-term kidney function, or survival, the Work Group anticipates substantial variability in patient values and preferences, supporting a Level 2 recommendation emphasizing shared decision-making.

Resource use and costs

The costs of intravenous amino acid infusion vary between different regions. There has not been a health economic evaluation of the resource use and costs of amino acid therapy in cardiac surgery patients, though in a patient-level meta-analysis, amino acid infusion was associated with a 1-day reduction in hospital length of stay.[446] The Work Group

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judged that the incremental costs of prophylactic intravenous amino acid administration vary between healthcare settings and the lack of evidence for benefit on high-cost, patient-important outcomes limits confidence that this strategy provides good value for money. Healthcare systems may differ in their decisions to adopt this intervention based on local costs, priorities, and the availability of alternative kidney-protection strategies.

Considerations for implementation

Implementation of amino acid infusion beginning before cardiac surgery and continuing for 3 days is feasible but requires planning and delivery into operating room workflows beginning before the start of surgery. Healthcare systems choosing to adopt this strategy should define clear protocols specifying patient selection, amino acid formulation, dosing, timing, and duration, consistent with regimens evaluated in clinical trials. Close collaboration among anesthesiology, surgery, critical care, and pharmacy teams may facilitate consistent and safe implementation. Use in people with advanced CKD should be approached with caution, given the limited evaluation in this population.

Rationale

Cardiac surgery with cardiopulmonary bypass is associated with a high incidence of AKI. By activating kidney functional reserve, amino acid infusion may compensate for the decrease in GFR associated with cardiac surgery, attenuating the rate of AKI. The strength of this recommendation was influenced by the uncertain effects on structural kidney injury and long-term kidney function.

Recommendation 3.5.2: We suggest remote ischemic preconditioning for patients at high risk for AKI undergoing cardiac surgery without propofol anesthesia to prevent AKI in children (*2D*) and adults (*2B*).

Remote ischemic preconditioning, triggered by brief episodes of ischemia and reperfusion before exposure to a potentially ischemic event, has been demonstrated to reduce the incidence of AKI and use of RRT in people undergoing cardiac surgery. However, this finding is limited to trials in which participants did not receive propofol anesthesia, which may attenuate its effect. It should be performed prior to or early during surgery by trained personnel. Evidence in children is limited, and the certainty of benefit is lower than in adults.

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Key information

Balance of benefits and harms

Remote ischemic preconditioning is a noninvasive intervention that appears safe, has a demonstrable effect on clinical outcome, and is inexpensive (Figure 10).

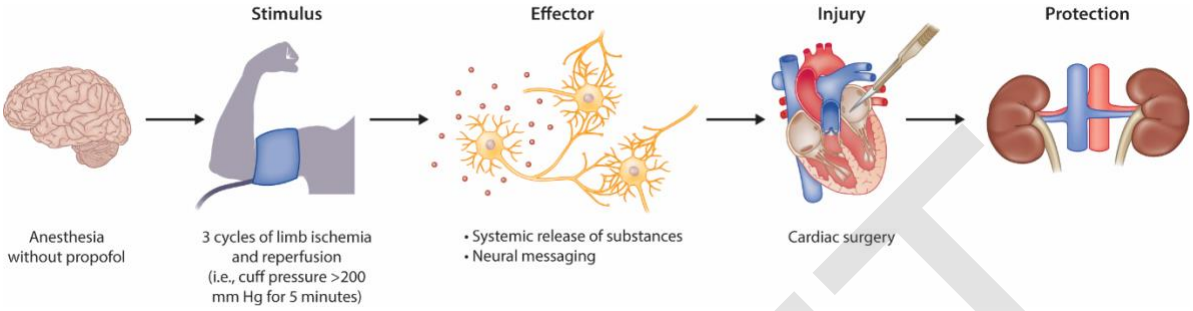

Figure 10 | Principles of remote ischemic preconditioning

However, it should not be applied to people with peripheral vascular disease. The risks of remote ischemic preconditioning are low, but it may cause discomfort if not done during anesthesia and may lead to petechial changes in the skin at the site of cuff inflation. It also requires time during perioperative care.

Studies have shown mixed results regarding protection of kidney function. Reasons for some of the controversial results include differences in patient populations (high-risk vs. low-risk populations), comorbidities, type of surgery, and remote ischemic preconditioning protocols. Further, some medications (e.g., propofol, sulfonamide) may mitigate the protective effects of remote ischemic preconditioning.

Meta-analysis of 8 RCTs comparing remote ischemic preconditioning with no remote ischemic preconditioning in 1003 adults undergoing cardiac surgery under general anesthesia without propofol showed a significantly lower incidence of postoperative AKI (RR: 0.71; 95% CI: 0.59–0.85) in the remote ischemic preconditioning group (Supplementary Table S54). Participants receiving remote ischemic preconditioning also had a lower risk of RRT initiation (RR: 0.50; 95% CI: 0.28–0.89) but there was no difference in mortality or $MAKE_{90}$.[447-456]

Data on the efficacy of remote ischemic preconditioning in children undergoing cardiac surgery without propofol derived from 1 RCT. The RCT compared remote ischemic preconditioning versus no remote ischemic preconditioning in 84 children undergoing cardiac surgery under general anesthesia without propofol and reported a lower incidence of AKI in those who received remote ischemic preconditioning, though the result did not achieve statistical significance for AKI or mortality (Supplementary Table S55).[457]

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In addition, a 2025 meta-analysis of 6 RCTs involving 1098 pediatric cardiac surgery patients who either received propofol or not found remote ischemic preconditioning significantly reduced AKI incidence (OR: 0.38; 95% CI: 0.25–0.60, p<0.00001), representing a 62% risk reduction.[458] This kidney benefit persisted despite moderate heterogeneity among studies (I^2=52%).

Certainty of evidence

There is moderate certainty of evidence that for adults undergoing cardiac surgery without use of propofol anesthesia, remote ischemic preconditioning reduces the risk of AKI and RRT initiation, without reported treatment-related adverse events.[447-456] The certainty of evidence was downgraded for some methodological limitations of the included studies.

There is very low certainty of evidence that for children undergoing cardiac surgery without use of propofol anesthesia, remote ischemic preconditioning may reduce the risk of AKI, but with unclear effect on mortality or adverse events.[457] The certainty of evidence was downgraded for sparse data with imprecise estimates and methodological limitations.

Values and preferences

This recommendation places a high value on preventing cardiac surgery-associated AKI. It places a lower value on the time required to perform remote ischemic preconditioning, which is noninvasive, usually performed after the patient has been anesthetized, and not associated with any specific harmful events. The Work Group judged that many people undergoing cardiac surgery would prefer remote ischemic preconditioning during anesthesia to prevent AKI as the additional discomfort would be minimal.

Resource use and costs

Remote ischemic preconditioning can be performed using a standard BP cuff and does not require specialized equipment. It can be integrated into routine perioperative workflows

Avoidance of propofol anesthesia may have implications for anesthetic selection and healthcare system protocols but is not expected to substantially increase costs. By reducing the incidence of postoperative AKI, remote ischemic preconditioning may decrease downstream resource utilization associated with RRT, prolonged hospitalization, and postoperative complications. Overall, the intervention is expected to be cost neutral or cost saving in most settings.

Considerations for implementation

Remote ischemic preconditioning should be delivered using a standardized protocol, typically consisting of repeated cycles of limb ischemia and reperfusion using a BP cuff, and

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performed prior to or early during anesthesia for cardiac surgery. Coordination between surgical, anesthesia, and perioperative teams is required to ensure appropriate timing and to avoid the use of propofol anesthesia which may attenuate the kidney-protective effect of the intervention.[459] Staff should be trained in correct cuff placement, inflation pressures, and monitoring to minimize local complications. Healthcare system protocols may facilitate consistent application, particularly in pediatric populations where cuff size and ischemia duration require adjustment.

Rationale

Remote ischemic preconditioning is a noninvasive intervention that induces transient limb ischemia to activate systemic protective pathways which may reduce ischemia–reperfusion injury in distant organs, including the kidney. RCTs and meta-analyses in adults undergoing cardiac surgery have demonstrated a reduction in postoperative AKI when remote ischemic preconditioning is used in the absence of propofol anesthesia.[459] Evidence in children is more limited, resulting in lower certainty, but available data suggest potential benefit without significant safety concerns. Given the low risk, minimal resource requirements, and potential to reduce AKI, RRT, and its downstream consequences; remote ischemic preconditioning represents a favorable preventive strategy in people undergoing cardiac surgery when anesthetic conditions are appropriate.

3.6 Hepatorenal syndrome-associated AKI

Recommendation 3.6.1: We recommend the use of vasoconstrictor therapy for adults with hepatorenal syndrome-associated AKI (*1C*).

Practice Point 3.6.1: The choice of vasoconstrictor should be based on the clinical care context and patient condition. Terlipressin or norepinephrine are preferrable therapies; midodrine with octreotide can be used as an alternative for adults if terlipressin and norepinephrine are unavailable.

People with hepatorenal syndrome-associated AKI typically tolerate RRT more poorly than people without liver disease due to relative systemic hypotension. Vasoconstrictor therapy has been shown to improve kidney function. For people with hepatorenal syndrome-associated AKI, improvement in kidney function may avoid RRT prior to liver transplantation with or without associated kidney transplantation. In people with hepatorenal syndrome-associated AKI who are not candidates for liver transplantation, improvement in kidney function may avoid RRT. Both norepinephrine and terlipressin can reverse AKI, but terlipressin has also been shown to reduce the incidence of RRT. However, terlipressin is associated with a higher incidence of ischemic and other adverse events, including pulmonary edema. The choice between terlipressin and norepinephrine is guided by local availability, clinician expertise, monitoring capabilities, and individual patient

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characteristics. Norepinephrine generally requires administration in settings with close hemodynamic monitoring, such as an ICU, whereas terlipressin may be administered outside the ICU in selected people. Individualized risk assessment and shared decision-making are essential when choosing between these treatment alternatives. Since terlipressin is not accessible in all countries, and treatment with norepinephrine often necessitates ICU admission, alternative therapies are required for hepatorenal syndrome-associated AKI in case of limited availability of ICU beds, the presence of contraindications to terlipressin therapy, as well as in countries where terlipressin is not approved for clinical use. The evidence supporting the efficacy of midodrine and octreotide is limited and generally of low certainty, and thus midodrine and octreotide should be considered only when terlipressin and norepinephrine are unavailable or cannot be administered. Healthcare professionals should recognize that response rates may be lower than with other vasoconstrictor therapies, and treatment should be reassessed regularly, particularly in people who fail to demonstrate early improvement in kidney function.

Key information

Balance of benefits and harms

The application of vasoconstrictor therapy in adults with hepatorenal syndrome-associated AKI is associated with improvement of kidney function and reversal of AKI. Meta-analysis of 12 RCTs comparing terlipressin versus placebo in 1559 adults with hepatorenal syndrome showed that participants treated with terlipressin had a significantly higher probability of reversal of hepatorenal syndrome (RR: 2.09; 95% CI: 1.79–2.45; Supplementary Table S56). Two RCTs included data on use of RRT and showed significantly lower RRT use in participants receiving terlipressin (RR: 0.77; 95% CI: 0.63–0.95). Seven studies included data on adverse events showing a significantly higher incidence in the terlipressin-treated cohort (OR: 2.28; 95% CI: 1.58–3.29), including serious gastrointestinal, cardiac, and respiratory complications. There was also a substantially greater proportion of participants receiving terlipressin who required therapy discontinuation but there was no difference in mortality.

Studies vary in patient selection, terlipressin dosing and escalation, and use of concomitant therapies, including fluid administration and concomitant use of albumin.[252] Given the increased risk of pulmonary edema, close monitoring of volume status during terlipressin therapy and adjustment of fluid and albumin administration is advised.

Norepinephrine and midodrine (with and without octreotide) are alternative vasoconstrictors for hepatorenal syndrome-associated AKI. Network meta-analysis showed norepinephrine reverses hepatorenal syndrome better than placebo (RR: 1.86; 95% CI: 1.40–2.47; Supplementary Table S54) but may not reduce risk of death (RR: 0.95; 95% CI: 0.77–1.18) with no indication of increase in serious adverse events.[460] Midodrine and octreotide

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may also reverse hepatorenal syndrome better than placebo (RR: 1.52; 95% CI: 0.98–2.35; Supplementary Table S55), but also may not reduce the risk of death (RR: 1.16; 95% CI: 0.78–1.72), also with no indication of increase in adverse events.[460]

A meta-analysis of 10 RCTs comparing norepinephrine and terlipressin in adults with hepatorenal syndrome showed no significant difference in recovery of kidney function (RR: 0.89; 95% CI: 0.74–1.06) or mortality (HR: 1.33; 95% CI: 0.87–2.00) but a significantly higher incidence of adverse ischemic events with terlipressin (RR: 3.33; 95% CI: 1.47–7.53; Supplementary Table S57).

Terlipressin is increasingly used worldwide. The increased risk of respiratory failure has led to regulatory warnings against using terlipressin in people with hypoxia and a recommendation to monitor respiratory status closely (Table 23).[461]

There are no RCTs comparing midodrine (alone) with placebo in hepatorenal syndrome-associated AKI. One RCT compared midodrine and octreotide with terlipressin (Supplementary Table S57). Based on network meta-analyses including various vasopressins, midodrine and octreotide had a lower incidence of kidney recovery than terlipressin (RR: 0.41; 95% CI: 0.19–0.86). There was no difference in mortality or incidence of serious adverse events (HR: 1.14; 95% CI: 0.42–3.11; Supplementary Table S59).[460]

Systematic reviews of studies comparing the use midodrine and octreotide to norepinephrine did not find significant differences in mortality (RR: 1.06; 95% CI: 0.78–1.44), reversal of hepatorenal syndrome-associated AKI (RR: 0.78; 95% CI: 0.56–1.10), or serious adverse events (RR: 1.49; 95% CI: 0.89–2.50; Supplementary Table S60).[460, 462]

Octreotide is typically administered as a subcutaneous injection, which is associated with minor discomfort. In some people, midodrine may cause bradycardia, though this is typically not hemodynamically significant due to the vasoconstrictor effect. Therefore, in most cases, the potential benefit for hepatorenal syndrome-associated AKI reversal exceeds the risks of harms associated with midodrine and octreotide treatment.

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Table 23 | Standardized vasoactive therapy in hepatorenal syndrome-associated AKI

Medication	Mode of administration	Recommended dose	Duration
Terlipressin	Continuous i.v. infusion (Preferred to reduce side effects)	Start at 2 mg/24h. If SCr does not decrease by >25% after 48h, increase every 24–48h up to a maximum of 12 mg/24h.	Until SCr returns to baseline (<1.5 mg/dl) or for a maximum of 14 days. Discontinue if no response by Day 4.
	i.v. bolus (Alternative)	0.5–1 mg every 4–6 hours. Increased to 2 mg every 4–6 hours if SCr does not decrease significantly.	Same as continuous infusion.
Noradrenaline	Continuous i.v infusion (Requires CVC)	0.5–3.0 mg/h titrated to achieve an increase in MAP of at least 10 mm Hg or to achieve a MAP >65–70 mm Hg.	Until reversal of hepatorenal syndrome or for a maximum of 14 days.
Midodrine + Octreotide	Oral Subcutaneous	7.5–15 mg every 8 hours 100-200 mcg every 8 hrs	Until reversal of hepatorenal syndrome; only consider if terlipressin is contraindicated or transfer to the ICU is not possible

AKI, acute kidney injury, ICU, intensive care unit; i.v., intravenous; MAP, mean arterial pressure; SCr, serum creatinine;

Certainty of evidence

There is moderate certainty of evidence that in adults with hepatorenal syndrome, terlipressin increases the likelihood of reversal of hepatorenal syndrome-associated AKI and decreases the risk of RRT compared with placebo, although, with a large increased risk of serious adverse events in the cardiac, respiratory, and gastrointestinal organ systems.[460, 463-467] The certainty of evidence was downgraded for some methodological limitations of the trials.

There is low certainty of evidence that in adults with hepatorenal syndrome, norepinephrine increases the likelihood of reversal of hepatorenal syndrome-associated AKI compared with placebo, does not affect mortality, and does not increase the risk of serious adverse events. The certainty of evidence was downgraded for some methodological limitations of the trials and imprecision.

There is very low certainty of evidence that, in adults with hepatorenal syndrome, combination therapy of midodrine and octreotide may increase the likelihood of reversal of hepatorenal syndrome-associated AKI compared with placebo but may not affect death or the risk of serious adverse events.[460] The finding is from a network meta-analysis that did not include any studies that directly compared midodrine plus octreotide to placebo. The

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certainty of evidence was, thus, downgraded for indirectness, in addition to methodological limitations of the included studies and imprecision in the effect estimates.

There is low certainty of evidence that in adults with hepatorenal syndrome, there is no difference in AKI outcomes or death between terlipressin and norepinephrine, but with high certainty of evidence that terlipressin is more likely to have ischemic adverse events. The certainty of evidence was downgraded for some methodological limitations of the trials and imprecision.

There is very low certainty of evidence that, in adults with hepatorenal syndrome, combination therapy of midodrine and octreotide is less likely to reverse hepatorenal syndrome-associated AKI than terlipressin. The finding is primarily from a network meta-analysis, which was statistically inconsistent with one direction.

There is low certainty of evidence of no difference in effect of midodrine and octreotide or norepinephrine on reversal of hepatorenal syndrome, death, or serious adverse events. Certainty of evidence was downgraded for methodological limitations and imprecision.[460, 462]

Values and preferences

The decision to initiate vasoconstrictor therapy requires shared-decision making with the patient, including a discussion about the potential benefit of avoiding RRT versus the risk of adverse effects and the potential need for transfer to the ICU. Whilst terlipressin can be given via a peripheral line or subcutaneously, it is associated with an increased risk of pulmonary oedema. Administration of norepinephrine often requires a central line and transfer to an ICU setting. Administration of midodrine and octreotide is relatively simple, though octreotide is often administered as a subcutaneous injection that may cause transient discomfort. However, for most patients, this is likely preferable to worsening hepatorenal syndrome-associated AKI, which may progress to a need for RRT and a high risk of mortality.

In some healthcare settings, kidney function impacts transplant prioritization for people who are candidates for liver transplantation, and an improvement in kidney function may portend longer waiting times for transplantation. For people who are not candidates for liver transplantation due to other comorbidities, the use of such therapies is likely to be life-prolonging.

This recommendation places a high value on preserving access to potentially beneficial therapy for hepatorenal syndrome-associated AKI in settings where first-line vasoconstrictors are unavailable or cannot be administered. The recommendation also

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reflects the value placed on flexibility and equity across diverse health care settings. Midodrine and octreotide are widely available and can be administered outside of ICUs, which may align with patient preferences to avoid higher levels of care. Given the very low certainty of evidence, the Work Group judged that most well-informed patients would accept the potential for modest or uncertain benefit in exchange for the possibility of kidney function improvement when no better-supported alternatives are available. Patients will likely prefer to receive either of these therapies, since progression of hepatorenal syndrome-associated AKI can lead to kidney failure, the need for RRT, other adverse outcomes, and death.

Resource use and costs

If a patient can avoid RRT for hepatorenal syndrome-associated AKI, this may be associated with decreased resource use and costs, though an economic analysis has not been published. The cost of terlipressin is higher than the cost of norepinephrine. The use of norepinephrine will typically require transfer to the ICU and placement of a central venous cannula or peripherally inserted central catheter, both of which are associated with resource use and costs.

Midodrine and octreotide are relatively inexpensive and more readily accessible than terlipressin or norepinephrine and require fewer resources for administration. These properties may reduce direct medication costs and the need for specialized staffing or facilities.

However, these potential cost savings may be offset by lower efficacy and uncertain clinical benefit, which could result in prolonged hospitalization, delayed kidney recovery, or increased need for RRT and escalation of care. The low certainty of evidence limits confidence in the cost-effectiveness of this regimen.

Considerations for implementation

The intermittent administration of terlipressin by peripheral line is logistically straightforward. Terlipressin can be administered in select non-ICU settings depending on institutional protocols and monitoring capacity. The administration of norepinephrine typically requires a central line or peripherally inserted central catheter placement for longer-term infusion and is typically administered in an ICU setting with continuous intravenous infusion and frequent BP and laboratory monitoring.

Terlipressin and norepinephrine require careful hemodynamic monitoring to avoid ischemic complications, arrhythmias, or excessive BP elevation. Healthcare professionals should assess contraindications, including significant cardiovascular disease, severe peripheral vascular disease, or uncontrolled hypertension. Dosing should be individualized,

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with early assessment of treatment response through changes in kidney function, urine output, and hemodynamics. Therapy should be adjusted or discontinued if adverse events occur or if no response is observed. In children, evidence is limited, and therapy should be guided by expert consultation and careful weight-based dosing.

Midodrine and octreotide do not require intravenous access for administration and can more readily be administered outside of the hospital setting. They should be implemented only as alternative therapy in people with hepatorenal syndrome-associated AKI when terlipressin and norepinephrine are unavailable or cannot be administered. This regimen is typically administered in non–ICU settings and requires coordinated oral and subcutaneous dosing, with careful titration of midodrine to achieve an increase in MAP. Blood pressure, kidney function, urine output, and serum electrolytes should be monitored closely, and healthcare professionals should remain vigilant for adverse effects such as bradycardia, hypertension, gastrointestinal intolerance, or ischemic complications.

Use of vasoconstrictor therapy should be integrated into a broader strategy for hepatorenal syndrome-associated AKI management, including albumin administration and timely evaluation for liver transplantation. Criteria for assessing a treatment response and for discontinuation or escalation of therapy should be established at the outset. Early consultation with hepatology and nephrology services may support appropriate patient selection and determination of suitability for alternative therapies, including RRT, and/or evaluation for liver transplantation.

Rationale

The rationale for vasoconstrictor use for hepatorenal syndrome-associated AKI is based on the ability to reverse splanchnic vasodilatation associated with advanced liver disease or cirrhosis, thereby improving renal perfusion and GFR. The ability to attenuate the risks associated with hepatorenal syndrome and to preserve and improve kidney function is important to prognosis and patient management, including potentially preventing the need for RRT.

Terlipressin, a vasopressin analog with predominant splanchnic vasoconstrictive effects, and norepinephrine, a potent systemic vasoconstrictor, have shown broadly comparable efficacy in improving kidney outcomes in appropriately selected adults. Although evidence for mortality benefit is inconsistent, improvement in kidney function is clinically meaningful, particularly as a bridge to liver transplantation or recovery from acute decompensation. The overall certainty of evidence in adults is low, reflecting variability in study design, outcome definitions, and adverse event reporting.

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When first-line agents such as terlipressin or norepinephrine are unavailable, midodrine, in combination with octreotide, is an alternative. Small trials and observational data suggest that this combination may improve kidney function in some people with hepatorenal syndrome-associated AKI, although the response rates are generally lower and less consistent than with terlipressin or norepinephrine. Evidence is limited by small sample sizes, heterogeneous patient populations, and variable outcome definitions, resulting in very low certainty of evidence.

The recommendation reflects a balance between potential benefits in reversing abnormal kidney function and potential adverse effects, including risks of vasoconstrictor therapy. The choice of agent should therefore be individualized based on clinical care context, patient condition, and available resources, recognizing that timely treatment of hepatorenal syndrome-associated AKI is a priority despite remaining uncertainties in the evidence base.

3.7 Tumor lysis syndrome-associated AKI

Practice Point 3.7.1: Volume expansion without urinary alkalinization using intravenous crystalloids should be done in children and adults with or at risk of tumor lysis syndrome.

Tumor lysis syndrome can occur spontaneously or in the setting of chemotherapy, typically in the context of leukemias/lymphomas and more rarely in solid cancers with relatively high cell turnover rates or massive cell burden. Uric acid from lysed tumor cells contributes to the pathogenesis of AKI due to precipitation in kidney tubules. Precipitation of calcium phosphate in renal tubules as a result of hyperphosphatemia may also be contributory. Hyperuricemia may also lead to decreased kidney blood flow through vasoconstriction and impaired autoregulation.[468] Hyperkalemia and metabolic acidosis from lysed cells can be life-threatening and necessitate urgent RRT. A number of classifications have been proposed to risk-stratify cancers into low, intermediate, and high risk for tumor lysis syndrome.[469, 470]

Consequently, efforts to prevent AKI are important for children with diseases or treatments carrying intermediate or high risks of tumor lysis syndrome. A predominant focus is on mitigating uric acid precipitation in kidney tubules. This can be aided by volume expansion, with the goal of increasing urine flow to at least 100 ml/hour in adults and preventing tubular obstruction, along with measures to decrease systemic uric acid concentrations. Crystalloids are recommended for volume expansion, although there is lack of evidence to support the selection of one fluid over another in this context. There is no evidence that alkalinization of urine reduces the risk of tumor lysis syndrome, but it may increase the development of calcium/phosphate crystals.

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Recommendation 3.7.1: In children and adults with or at high risk of tumor lysis syndrome, we recommend rasburicase over allopurinol or febuxostat, if not contraindicated due to glucose 6-phosphate dehydrogenase (G6PD) deficiency (*1B*).

Practice Point 3.7.2: In children and adults at lower risk of tumor lysis syndrome, or when rasburicase is contraindicated or inaccessible, xanthine oxidase inhibitors may be used.

Rasburicase is a recombinant form of urate oxidase, which metabolizes uric acid to the much more soluble allantoin. In contrast, allopurinol and febuxostat inhibit xanthine oxidase to prevent the formation of uric acid from hypoxanthine and xanthine. Consequently, allopurinol and febuxostat are not effective when uric acid is already present since these agents do not lower uric acid concentration. Rasburicase may prevent the need for RRT in people at high risk and has the greatest benefit for people with high baseline uric acid levels, rapidly proliferative or highly chemosensitive malignancies, high tumor burden, or impaired kidney function at presentation. Screening for glucose-6-phosphate dehydrogenase (G6PD) deficiency is recommended before administration when feasible, as rasburicase is contraindicated in people with G6PD deficiency. In people at lower risk of tumor lysis syndrome, or when rasburicase is contraindicated or unavailable, xanthine oxidase inhibitors (allopurinol or febuxostat) may be used. Cost, availability, and institutional protocols may influence agent availability and selection.

Key information

Balance of benefits and harms

The majority of evidence for prophylaxis and treatment of tumor lysis syndrome comes from studies in children, since they are more likely to have cancers that put them at high risk of tumor lysis syndrome. Rasburicase is a recombinant urate oxidase that enzymatically converts uric acid to allantoin, a highly soluble metabolite readily excreted by the kidney. This mechanism allows rapid and profound reduction in serum uric acid levels, including clearance of preexisting hyperuricemia. The side effect profile of rasburicase includes disseminated intravascular coagulopathy and severe allergies. People with G6PD deficiency are at risk of methemoglobinemia. In contrast, allopurinol and febuxostat inhibit xanthine oxidase and reduce the formation of new uric acid but do not eliminate circulating uric acid already present at the time of treatment initiation. Their onset of action is slower, and they may lead to accumulation of xanthine and hypoxanthine.

Meta-analysis of 4 RCTs comparing rasburicase versus allopurinol in children with tumor lysis syndrome showed that those treated with rasburicase had a significantly lower risk of needing RRT (RR: 0.27; 95% CI: 0.10–0.76) and a significantly lower risk of tumor

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lysis syndrome related mortality (RR: 0.05; 95% CI: 0.0–0.90) but also a significantly higher risk of serious adverse events (RR: 6.20; 95% CI: 1.14–33.65), which included disseminated intravascular coagulopathy and methemoglobinemia (Supplementary Table S61).[471-475]

In people with G6PD deficiency, the generation of hydrogen peroxide as part of the metabolism of uric acid by rasburicase can cause severe hemolytic anemia and methemoglobinemia. Thus, screening for G6PD deficiency is recommended in newborns and individuals of African, Asian, Mediterranean, or Middle Eastern descent before administration when feasible. Allergic reactions are also relatively common.

The evidence for prevention and management of tumor lysis syndrome in adults is limited. The challenge with extrapolating the effects of these agents on adults is that adult populations are generally at lower risk of life-threatening tumor lysis syndrome. Rasburicase is often reserved for administration in adults only when uric acid levels exceed a predetermined threshold because of higher cost and risks of adverse reactions.

In people at low risk of tumor lysis syndrome, or when rasburicase is contraindicated or unavailable, xanthine oxidase inhibitors may be used. Allopurinol can be considered in those with low or intermediate risk of tumor lysis syndrome. Prescribers should be aware of the high incidence of skin reactions with allopurinol. Screening for allopurinol hypersensitivity with the HLA-B*58:01 genetic allele should be considered before initiating therapy, when possible, particularly for people of Han Chinese, Thai, or Korean descent. Hypersensitivity reactions, including Stevens-Johnson syndrome, are also more common with allopurinol. Finally, allopurinol has a number of important drug-drug interactions that must be considered during its administration.

An alternative xanthine oxidase inhibitor with fewer interactions is febuxostat. However, there have been reports of hypersensitivity reactions, and an increased risk of mortality from major cardiovascular events with febuxostat. The safety and efficacy of febuxostat in children has not been established.

Certainty of evidence

There is moderate certainty of evidence that, in children with tumor lysis syndrome, rasburicase greatly reduces the risk of death due to tumor lysis syndrome and the risk of AKI requiring RRT compared with allopurinol, but with no evidence of an effect on overall mortality.[471-475] However, rasburicase increases the risk of serious adverse events compared with allopurinol. The certainty of evidence was downgraded for very serious methodological limitations across trials but was upgraded due to the very large effect sizes for most outcomes. The certainty of evidence for use of rasburicase in adults with tumor lysis

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syndrome was downgraded to low due to indirectness, since there were no eligible trials in adults.

Values and preferences

This recommendation places a high value on the prevention of life-threatening complications of tumor lysis syndrome, including AKI requiring RRT, but also cardiac arrhythmias, seizures, and death, through rapid and effective reduction of serum uric acid levels. The Work Group judged that patients and healthcare professionals would generally prioritize immediate and reliable uric acid control in those at high risk or with tumor lysis syndrome over considerations of higher acquisition cost and the need for parenteral administration associated with rasburicase.

However, this recommendation also places a high value on safety in people with G6PD deficiency, in whom rasburicase may cause severe hemolysis and methemoglobinemia. In settings where G6PD status is unknown and testing is not readily available; healthcare professionals and patients may choose alternative urate-lowering strategies until deficiency is excluded.

Resource use and costs

Cost, availability, and healthcare system protocols may influence agent selection and dosing strategies. The Work Group recognized that the cost of rasburicase is greater than that of allopurinol or feboxustat on a per-dose or per-treatment-course basis. Further, rasburicase requires intravenous administration and appropriate laboratory handling of blood samples on ice for uric acid measurement, which may increase direct and indirect healthcare costs compared with orally administered alternatives.

The prevention of AKI requiring RRT with its associated costs may make use of rasburicase cost-effective. The Work Group recognized that rasburicase is substantially more expensive than xanthine oxidase inhibitors (allopurinol and febuxostat) on a per-dose and per-treatment-course basis. However, a cost effectiveness analysis from the U.S. suggested that rasburicase was associated with significantly shorter ICU and overall hospital stays and lower total inpatient costs than allopurinol for people with tumor lysis syndrome.[476] Cost-effectiveness is likely to vary according to baseline tumor lysis syndrome risk, local drug pricing, dosing strategies, and healthcare system structure. In people at low risk of tumor lysis syndrome, the incremental benefit of rasburicase over allopurinol or febuxostat is likely small, and the higher cost may not be justified. In contrast, in people at high risk of tumor lysis syndrome or with marked hyperuricemia, rasburicase is more likely to be cost-effective due to reduction in downstream complications.

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Availability of rasburicase may be limited in some regions, and access to G6PD testing may further influence resource use. In resource-constrained settings, cost and access considerations may necessitate prioritization of rasburicase for those at highest risk, with allopurinol or febuxostat used in lower-risk patients.

Considerations for implementation

Successful implementation of this recommendation requires systematic risk stratification for tumor lysis syndrome in children and adults with malignancy, ideally prior to initiation of cytotoxic therapies. Institutions should establish standardized protocols to identify people at intermediate and high risk of tumor lysis syndrome. Early recognition is essential to allow timely administration of rasburicase before or at the onset of biochemical abnormalities.

Rasburicase should not be administered to people with G6PD deficiency due to the risk of severe hemolysis and methemoglobinemia. Screening for G6PD deficiency should be performed in populations with higher prevalence, when feasible, and urgently when clinical suspicion exists. In situations where G6PD status is unknown and testing is not immediately available, healthcare professionals should carefully weigh risks and benefits, particularly in people at lower risk.

Healthcare systems should ensure availability of rasburicase in centers treating people at high risk of tumor lysis syndrome. Institutional protocols may include predefined dosing to optimize efficacy and cost-effectiveness. Clear guidance regarding repeat dosing criteria based on serial uric acid measurements and clinical response should be established.

Appropriate laboratory handling of blood samples is critical when monitoring uric acid levels in people receiving rasburicase, as *ex vivo* uric acid degradation can lead to falsely low measurements. Blood samples should be collected in prechilled tubes, transported on ice, and analyzed promptly according to manufacturer and laboratory guidance.

Rasburicase should be integrated into a comprehensive tumor lysis syndrome prevention and management strategy that includes intravenous hydration, careful monitoring of electrolytes and kidney function, and prompt management of associated electrolytes abnormalities including hyperkalemia, hyperphosphatemia, and hypocalcemia. Interdisciplinary coordination among oncology, nephrology, pharmacy, and laboratory services is essential.

Rationale

The recommendation to use rasburicase in children and adults at risk or with tumor lysis syndrome is based on the effectiveness at preventing the need for RRT but close

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monitoring for serious adverse effects is needed. Uric acid plays a central role in the pathogenesis of tumor lysis syndrome-associated AKI through intratubular crystal precipitation, tubular obstruction, and renal vasoconstriction. The risk and severity of AKI correlate with the magnitude and rapidity of uric acid elevation. Accordingly, prompt, and effective urate control is a cornerstone of tumor lysis syndrome prevention and management.

RCTs and comparative studies in both pediatric and adult populations with hematologic malignancies consistently demonstrate that rasburicase lowers uric acid more rapidly and more completely than allopurinol. Evidence also supports reduced rates of laboratory tumor lysis syndrome and need for RRT with rasburicase in high-risk populations.

In people at low or intermediate risk of tumor lysis syndrome, the absolute risk of severe hyperuricemia and AKI is lower. In this setting, prophylactic reduction of uric acid production with allopurinol or febuxostat is generally sufficient, and the incremental benefit of rasburicase is likely small.

The recommendation therefore reflects a risk-adapted approach. In children and adults at high risk of tumor lysis syndrome, or with established laboratory or clinical tumor lysis syndrome, the benefits of rapid and reliable urate reduction with rasburicase outweigh considerations related to cost and intravenous administration. In contrast, for those at low or intermediate risk, xanthine oxidase inhibitors represent reasonable and effective alternatives for prevention.

3.8 Rhabdomyolysis- and hemolysis-associated AKI

Practice Point 3.8.1: Use intravenous crystalloids for volume expansion in children and adults at risk of or with heme pigment nephropathy due to rhabdomyolysis or hemolysis.

Myoglobin and hemoglobin are endogenous nephrotoxic substances that can precipitate in kidney tubules and cause acute tubular injury in the setting of rhabdomyolysis and intravascular hemolysis, respectively. People with rhabdomyolysis and hemolysis should be monitored closely for the development of hyperkalemia or metabolic acidosis that also accompany muscle and breakdown of red blood cells and may increase the risk of requiring RRT. There are no specific pharmacotherapies to enhance metabolism of myoglobin or hemoglobin. The mainstay of therapy is volume expansion to prevent precipitation in kidney tubules, with close monitoring for fluid overload, which may develop rapidly if patients become oliguric. There is limited data to support the selection of one crystalloid fluid over another in this setting.

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In people with rhabdomyolysis, the use of isotonic bicarbonate solutions has been proposed to increase the solubility of myoglobin but the limited data do not support this practice.[477, 478] A strategy to augment urine output using mannitol or loop diuretics is not advised.

3.9 Nutritional intervention in AKI

Practice Point 3.9.1: Nutrition should be provided preferentially via the enteral route in children and adults at risk of or with AKI or AKD.

At present, there is limited data to guide the provision of nutritional support in adults with or at risk of AKI or AKD.[479] Many nutrition guidelines are largely opinion based. Despite these limitations, it is clear that enteral nutrition is the preferred form of nutritional support for hospitalized children and adults, with provision via a feeding tube if oral feeding is not possible. Enteral nutrition is thought to decrease gut atrophy and maintain gut integrity, which decreases bacterial and endotoxin translocation.

AKI is a major risk factor for gastrointestinal bleeding, and enteral nutrition is thought to reduce the risk of stress ulcers and consequently gastrointestinal bleeding. Although the enteral route is preferred, more recent clinical trials (Enteral versus parenteral early nutrition in ventilated adults with shock [NUTRIREA-2]) suggest that the risks of parenteral nutrition (e.g., infection) are often overestimated, so if the enteral route cannot be used or enteral nutrition is not tolerated, parenteral nutrition is preferable to no nutrition.[480]

Practice Point 3.9.2: Avoid restriction of protein intake with the aim of preventing or delaying initiation of RRT in children and adults with AKI or AKD.

Protein hypercatabolism, driven by inflammation, stress and acidosis, is common among critically ill children and adults. Those with AKI are at high risk of malnutrition but the optimal amount of protein supplementation is unknown. Nutritional management should aim to supply sufficient protein to maintain metabolic balance. There is little evidence that hypercatabolism can be overcome simply by increasing protein intake.

Restricting protein can exacerbate muscle wasting and malnutrition, leading to poor outcomes. Studies show that protein intake does not delay kidney recovery but rather supports growth and healing.[481] Hence, nutritional protein administration should not be restricted as a means to attenuate the rise in blood urea nitrogen associated with declining GFR.

Children with AKI are at high risk of protein-energy malnutrition, particularly in ICU settings, where nutritional deficits can weaken immune function and prolong

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hospitalization.[482] Guidelines from the Pediatric Renal Nutrition Taskforce and the ADQI recommend age-appropriate protein and caloric intake rather than generalized restrictions, ensuring that children receive sufficient nutrition to prevent deficits and support recovery.[483]

Practice Point 3.9.3: Excessive protein intake should be avoided in adults with AKI or AKD.

Given the association of protein-calorie malnutrition with adverse outcomes in critically ill adults, there has been significant interest in protein supplementation. A large, pragmatic RCT compared the impact of high protein intake (≥2.2 g/kg/day) versus usual protein intake (≤1.2 g/kg/day) in critically ill adults on mechanical ventilation.[484] There was no difference in the proportion of participants discharged alive by day 60 (46.1% in the high protein arm vs. 50.2% in the usual protein arm, p=0.27). However, participants with AKI who were randomized to high protein intake had a higher mortality and longer time to hospital discharge.

In a *post hoc* analysis of the Nephro-Protective trial, participants with normal baseline kidney function had lower mortality with amino acid supplementation to achieve a total protein intake of 2 g/kg/day, whereas those with abnormal kidney function at study entry did not have harm from amino acid supplementation, but also had no benefit.[485]

These trials suggest that excessive protein intake should be avoided in adults with AKI or AKD. Although protein and amino acid losses increase with continuous renal replacement therapy (CRRT) and peritoneal dialysis (PD), the extent depends on the dialysis prescription. It is also unclear how protein intake should be adjusted.

Practice Point 3.9.4: Caloric targets do not need to be changed due to AKI or AKD in children or adults, unless they are receiving RRT.

Adequate nutritional support is important to support recovery from critical illness. Although many diseases associated with AKI or AKD (e.g., sepsis) will increase metabolic demand and catabolism, metabolic requirements should take into consideration the disease processes associated with AKI or AKD. Caloric targets do not need to be restricted in the context of AKI or AKD. When feasible, indirect calorimetry should be considered to measure energy expenditure and metabolic rates. Furthermore, to avoid overfeeding, calories provided from RRT fluids and citrate should be incorporated into caloric targets for children and adults receiving RRT.

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Practice Point 3.9.5: Regular review and supplementation of water-soluble vitamins and micronutrients should be considered in children and adults receiving continuous RRT (CRRT).

CRRT is associated with increased loss of water soluble vitamins (B complex vitamins and vitamin C) and micronutrients in the effluent fluid.[486] In a scoping review that analyzed 35 publications with focus on micronutrient loss during RRT, carnitine, copper, and selenium along with vitamins B1 and C were identified as micronutrients where deficiency/loss was commonly observed.[487] Because of variability in CRRT modality, dose, membrane characteristics, duration of therapy, nutritional intake, and patient-specific factors, the risk and magnitude of micronutrient losses are heterogeneous. Routine supplementation with standard multivitamin preparations may not fully compensate for ongoing losses in people receiving prolonged or high-effluent-dose CRRT, while indiscriminate high-dose supplementation without monitoring may risk accumulation of certain trace elements.

Monitoring strategies should be individualized based on duration and intensity of CRRT, nutritional status, and clinical course. Measurement of selected micronutrients (e.g., thiamine, vitamin C, selenium, zinc) may be considered in people receiving prolonged CRRT, those with limited nutritional intake, or when clinical features raise suspicion of deficiency.

In settings where laboratory measurement is not readily available, empiric supplementation with water-soluble vitamins at doses exceeding standard daily requirements may be reasonable, particularly for thiamine. However, whether routine supplementation is beneficial has not been investigated in an RCT.

3.10 AKI in pregnancy

Practice Point 3.10.1: Pregnant women with AKI or AKD require specific treatments, including consideration of early delivery.

AKI during pregnancy and following childbirth is an important obstetric complication, with distinct etiologies shaped by the interplay of maternal physiology and pregnancy-specific pathologies. Globally, pregnancy-related AKI affects approximately 2% of pregnancies. with incidences as low as 0.08%–0.12% in high income countries.[488] However, rates remain 20–100-fold higher in low- and middle-resource settings.[489] In the U.S., pregnancy-related AKI incidence tripled between 2006 and 2015, fueled by rising maternal age and comorbidities, including diabetes and hypertension.[490] Racial inequities persist, with Black and Native American women facing 52% and 45% higher risks, respectively, compared to White women.

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The causes of AKI in pregnancy may be due to pregnancy specific disorders, including preeclampsia, hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome, acute fatty liver of pregnancy, thrombotic microangiopathies, severe hemorrhage, sepsis, and factors independent of pregnancy. These conditions may progress rapidly and are associated with substantial maternal and fetal morbidity and mortality. Identifying the underlying etiology is important to guide management, including consideration of early delivery.

Management of AKI or AKD in pregnancy differs from nonpregnant populations in several important respects.[491] Maternal stabilization must occur concurrently with continuous assessment of fetal well-being. Volume management requires careful attention to the altered physiologic state of pregnancy and the risk of pulmonary edema, particularly in preeclampsia. Blood pressure targets may differ, and medications must be selected with consideration of fetal safety. Nephrotoxic agents and drugs contraindicated in pregnancy should be avoided.

In severe preeclampsia, HELLP syndrome, or acute fatty liver of pregnancy, maternal abnormal kidney function may improve only after delivery and delivery of the fetus and placenta represents definitive therapy. Similarly, persistent maternal deterioration (e.g., worsening kidney function, refractory hypertension, pulmonary edema, or progressive thrombocytopenia) or evidence of fetal compromise may necessitate early delivery, balancing gestational age, and neonatal risks against maternal safety. The timing of delivery should be individualized and determined collaboratively by obstetrics, maternal–fetal medicine, nephrology, neonatology, and critical care teams.[492, 493]

RRT is required in 30% of women with pregnancy-related AKI for maternal or fetal indications. When indicated, RRT should not be delayed due to pregnancy. Intensified dialysis regimens may be required to optimize maternal metabolic control and improve fetal outcomes. Anticoagulation strategies and modality selection should consider bleeding risk, hemodynamic stability, and gestational age.

3.11 Environmental and tropical AKI

Practice Point 3.11.1: For children and adults presenting with AKD or AKI in tropical and subtropical regions, evaluate for region-specific infectious and environmental causes and initiate early disease-specific therapy in addition to standard supportive management of AKI.

Given the diverse etiologies of tropical AKI, including infectious and environmental causes (e.g., malaria, leptospirosis, dengue, scrub typhus, envenomation, hemolysis, rhabdomyolysis, and diarrheal illness), early recognition through clinical suspicion and

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targeted diagnostic tests, prompt kidney protective measures and use of appropriate infection-specific therapy, antivenom and management of hemolysis/rhabdomyolysis and timely initiation of RRT are critical elements of management of AKI in tropical and subtropical regions. Prevention also relies on improving public health measures (e.g., safe water, sanitation, vector control), regulation of traditional remedies, and expanding access to effective medical care, especially in resource-limited settings.

Tropical infections

AKI developing in the setting of locally prevalent infections is a significant and distinct clinical challenge in tropical regions.[494] Infections account for 40%–44% of AKI cases in tropical low- and middle-resource settings.[495] The tropical climate, characterized by high temperatures and humidity, favors the proliferation of pathogens (e.g., *Plasmodium* and *Leptospira sp*, spirochetes, dengue virus, and waterborne bacteria) and vectors (e.g., mosquitoes, mites, etc.) responsible for a wide array of infections that can precipitate AKI. Socioeconomic and public health challenges, such as poor sanitation, limited access to clean water, and under-resourced healthcare systems, further amplify the risk and burden of infection-associated AKI.[494, 496, 497] Tropical infection-associated AKI is mostly community-acquired and more frequently affects younger, previously healthy people.

Specific tropical infections associated with AKI include malaria, leptospirosis, dengue and other viral hemorrhagic fevers, scrub typhus, and yellow fever, human immunodeficiency virus infection and diarrheal diseases (Table 24).[494, 496, 497] Making an accurate diagnosis of the specific tropical infection causing AKI is critical for ensuring effective management but is challenging due to overlapping clinical features such as fever, jaundice, and oliguria, and limited access to laboratory diagnostics in resource-limited settings.[498] Reliance on traditional healers and/or delayed presentation to hospitals may exacerbate the problem, often resulting in people arriving with established and severe AKI.

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Table 24 | Tropical infections causing AKI

Infection	World region where prevalent	Common clinical presentations	Mechanism of AKI
Malaria (Plasmodium falciparum, vivax)	Southeast Asia, Central America, Africa	Fever, chills, splenomegaly, jaundice, hemolysis	ATN, hemoglobinuria-induced injury, cytoadherence causing microvascular obstruction
Leptospirosis	South Asia, Latin America	Fever, jaundice, myalgia, conjunctival suffusion, thrombocytopenia	Direct tubular invasion, interstitial nephritis, volume depletion, rhabdomyolysis
Dengue	Tropical and subtropical regions worldwide	Fever, hemorrhagic manifestations, thrombocytopenia, myalgia, vomiting	Hemodynamic instability, rhabdomyolysis, immune complex deposition, ATN
Scrub typhus	South Asia	Fever, maculopapular rash, eschar, thrombocytopenia	Direct tubular invasion, interstitial nephritis, vasculitis
Enteric fever (Typhoid)	Tropical regions	Fever, abdominal pain, diarrhea	Sepsis-induced ATN, volume depletion
Hantavirus	Tropical regions	Fever, severe respiratory symptoms, ARDS	ATN, capillary leak syndrome
HIV-associated AKI	Tropical regions with high HIV prevalence	Variable, often with opportunistic infections	Direct viral injury, drug nephrotoxicity, immune complex glomerulonephritis
Rickettsiosis	Tropical regions	Fever, rash, eschar	Vasculitis, interstitial nephritis
Brucellosis	Tropical regions	Fever, splenomegaly	Immune complex glomerulonephritis, sepsis
Acute diarrheal illnesses	Tropical regions	Fever, diarrhea, dehydration	Prerenal AKI due to volume depletion, sepsis
Yellow fever	Tropical regions of Africa and South America	Fever, jaundice, hemorrhage, multi-organ failure	ATN, AIN, vascular thrombosis, hemorrhagic lesions
Viral hemorrhagic fevers (e.g., Ebola, Marburg, Lassa, Crimean-Congo hemorrhagic fever)	Africa, Asia, parts of Europe (Crimean-Congo)	Fever, hemorrhage, shock, multi-organ failure	ATN, capillary leak syndrome, volume depletion, rhabdomyolysis, immune-mediated injury

AIN, acute interstitial nephritis; AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; ATN, acute tubular necrosis; HIV, human immunodeficiency virus.

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Tropical infection-related AKI has a mortality rate of 12%–30%, depending on the infection and access to care. Survivors often face long-term consequences, including chronic kidney disease.[499]

Management is complicated by the scarcity of RRT facilities, especially in rural areas. Hemodialysis, the standard treatment for severe AKI, is often unavailable or unaffordable, making peritoneal dialysis a more feasible alternative in many tropical settings. Prompt treatment of the underlying infection is crucial: antimalarials for malaria, antibiotics for leptospirosis, and supportive care, including fluid management for dengue and diarrheal diseases.

Practice Point 3.11.2: For children and adults presenting with AKD or AKI in regions where traditional medicines and toxic chemicals are used, include AKI due to toxins in the differential diagnosis.

AKI caused by plant and industrial toxins represents a significant health issue, particularly in regions where traditional medicine is integral to healthcare and the availability and use of chemicals (e.g., pesticides) is often unregulated.[500] Epidemiological studies indicate that 35% of AKI cases in some developing countries are linked to plant-derived remedies. A large proportion of the rural populations in Asia, Africa, and Latin America rely on traditional therapies and are disproportionately affected. The WHO estimates that 80% of the population of Asian and some African countries presently use herbal medicine for some aspect of primary healthcare. In developing countries like India, 65% of rural communities still use a traditional form of medicine to fulfill their primary healthcare needs (https://tinyurl.com/3pnkfcbc).

Consumption of certain plant components, common in certain cultures may cause AKI if they are not processed properly (e.g., djenkol, impila, *Aveorrhea*). Agricultural and industrial workers have access to pesticides (e.g., paraquat and aluminum phosphide) and industrial chemicals (e.g., copper sulfate) which are often used for suicidal purposes and cause AKI.

Identifying plant and chemical toxin-induced AKI is challenging due to a number of reasons (Table 25): underreporting (cultural trust in traditional healers or belief in the benign nature of the source of toxin), nonspecific nature of symptoms (i.e., mimicking gastroenteritis, rhabdomyolysis), contamination with other substances such as heavy metals (e.g., mercury, lead) or adulterants (e.g., ethylene glycol).

Management usually entails supportive therapy, hydration, hemodynamic support, and RRT if required. Hurdles include poor awareness, a lack of antidotes and limited access

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to RRT. Addressing AKI will require multidisciplinary strategies, including public education, regulation of herbal products, and integrating traditional healers into healthcare systems.

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Table 25 | Common plant and chemical toxins causing AKI

Substance	Type (source)	Clinical manifestations	Indication of use or exposure in the context of AKI
Aloe capensis (Cape aloe)	Plant	Abdominal pain, hemorrhagic gastroenteritis, ATN	Hypertension, arthritis
Callilepis laureola (Impila)	Plant	Abdominal pain, diarrhea, ATN, oliguric AKI, hepatic dysfunction, hypoglycemia, metabolic acidosis	To induce fertility, to correct impotence, and to ward off "evil spirits"
Catha edulis (Khat)	Plant	ATN	Khat leaf chewing is a local habit in some African populations; also used as a folk remedy for obesity and depression.
Colchicum autumnale (Meadow saffron)	Plant	Gastroenteritis/multiorgan failure/hepatic injury/shock/AKI	Used for acute gouty arthritis. Suicidal colchicine tablet overdose is the most common cause of colchicine poisoning.
Glycyrrhiza glabra (Licorice)	Plant	Contains glycyrrhetinic acid - can lead to hypokalemia, rhabdomyolysis, AKI, pseudoaldosteronism	Cough remedy
Amanita phalloides (Toxic mushrooms)	Plant	Gastroenteritis, hepatic failure, AKI	Accidental ingestion, anticancer, anti-inflammatory
Carica papaya (Papaya leaf)	Plant	Severe mucositis and gastritis leading to severe dehydration causing prerenal AKI	To increase platelet count in dengue fever
Tamaris orientalis (Takaout el badia)	Plant	Can cause rhabdomyolysis and AKI	Henna for hair dyeing
Hypericum perforatum (St. John's wort)	Plant	Induces cytochrome P450 enzyme-drug interactions and AKI	Used for depression and menopausal symptoms
Propolis (Honeybee product)	Plant/animal product	AIN	Used as antiseptic/ anti-inflammatory agent and hepatoprotective substance in South America
Carp (Fish gallbladder extract)	Animal product	Can lead to watery diarrhea, jaundice, bradycardia, hypotension, oligoanuria and AKI	Used in folk therapies in parts of Asia
Caesalpinia decapetala (Cat's claw)	Plant	AIN	An herbal remedy used in Peru as anti-inflammatory drug for rheumatism, systemic lupus erythematosus, cirrhosis
Cerbera thevetia (Yellow oleander)	Plant	ATN	Used as folk remedy for heart conditions, asthma, epilepsy, cancer, and painful menstrual periods

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Cupressus funebris (Mourning cypress)	Plant	ATN, interstitial nephritis, and hemoglobin casts	Used as herbal remedy for bleeding piles and painful menstrual cycles
Securidaca longepedunculata (Wild wisteria)	Plant	Contains salicylates - can cause ischemic kidney damage / cortical necrosis and AIN	Used as folk remedy for dysmenorrhea and venereal diseases
Euphorbia paralias (Spurge)	Plant	ATN	Used as traditional medicine as an anti-inflammatory agent, a purgative and for its local anesthetic property
Crotalaria laburnifolia (Bird flower)	Plant	Acute tubular injury	Used for dysmenorrhea and abortifacient
Archidendron pauciflorum (Djenkol beans)	Plant	Djenkolism - spasmodic suprapubic and/or flank pain, urinary obstruction, and AKI	Local delicacy in Southeast Asia
Sobi-lobi (Datura)	Plant	Contains anticholinergic substances; urinary obstruction and AKI	Consumed for its hallucinogenic properties
Salix daphnoides (Willow bark)	Plant	The bark contains salicylate, which is metabolized in the body to salicylate; renal papillary necrosis	Used for pain/headache and inflammatory conditions in China and Europe
1,2-Dibromo-3-Chloropropane (DBCP)	Chemical (pesticide)	ATN observed in animal studies, potential human carcinogen	Agricultural pesticide/fumigant with nematocidal activity
Heavy metals (Cadmium, uranium, lead, mercury)	Chemical (environmental)	ATN in acute intoxication, over 90% absorption in proximal tubular cells	Environmental and industrial exposure
Paraquat	Chemical (herbicide)	AKI, often with lung involvement and multiple organ failure	Agricultural herbicide, intentional or accidental ingestion
Methanol	Chemical (solvent)	Metabolic acidosis leading to AKI, often with visual and neurological impairment	Industrial solvent, accidental or intentional ingestion
Organophosphorus compounds	Chemical (pesticide)	Ischemic ATN due to volume loss or systemic toxicity	Agricultural pesticide, intentional or accidental exposure
Copper sulphate	Chemical (poison)	Systemic and local toxicity, acute tubular necrosis, hemolysis leading to AKI	Industrial use, accidental or intentional ingestion
Acetic Acid	Chemical (acid)	Coma, shock, hemolysis, anuric kidney failure, pigment nephropathy	Used in food preservation, accidental ingestion
Arsenic	Chemical (poison)	AKI with acute hemolysis, systemic toxicity	Historical medical use, pesticide, intentional poisoning

AIN, acute interstitial nephritis; AKI, acute kidney injury; ATN, acute tubular necrosis

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Practice Point 3.11.3: For children and adults presenting with AKD or AKI following prolonged exposure to high temperatures, consider heat injury as a cause of AKI.

Heat injury, especially from heatstroke, can lead to AKI through dehydration, hypotension, and direct tubular damage.[501-503] Outdoor workers, particularly in tropical regions, are highly vulnerable due to prolonged exposure to high temperatures and intense physical labor. Those with limited access to water face an even greater risk. Workers in construction, agriculture, and similar fields often lack consistent breaks or hydration resources, especially in areas with poor infrastructure or employer oversight. Climate change makes this worse by driving up temperatures and the frequency of heatwaves, putting these workers at higher risk of heat-related kidney damage. Recurrent episodes of AKI can progress to CKD and have been implicated in the genesis of CKD of unknown etiology, especially in Central America and South Asia.[504, 505]

Prevention entails practical steps like staying hydrated by drinking water regularly, avoiding strenuous work during the hottest parts of the day, taking rest breaks in shaded areas, and gradually acclimating to hot environments to build tolerance. For outdoor workers, employers should provide water access, enforce breaks, and train staff to spot early heat stress signs like dizziness.

3.12 Considerations specific in children

3.12.1 Hemodynamic management

Practice Point 3.12.1.1: Use age-appropriate blood pressure targets to guide hemodynamic management in children at risk or with AKI.

Avoidance of hypotension is a critical component of hemodynamic management. The Surviving Sepsis Campaign defines pediatric hypotension by age-based systolic thresholds (e.g., <50 mm Hg for infants <12 months, <60 mm Hg for children 1–5 years, and <70 mm Hg for those >5 years), which are used to trigger resuscitative efforts in septic shock and have been widely adopted in pediatric critical care.[323]

Even brief durations of profound hypotension, defined by systolic BP below the first percentile for age, sex, and height, are independently associated with increased risk of new or persistent AKI in children with sepsis. In a large retrospective cohort study, the odds of developing Stage 2 or 3 AKI increased by 9% for every doubling in time spent under this severe hypotensive threshold, independent of other risk factors.[506] This association was not observed when hypotension was defined by Pediatric Advanced Life Support thresholds, suggesting that individualized, percentile-based targets may be more sensitive for identifying kidney hypoperfusion risk. Additionally, longer duration of hypotension was associated with fewer AKI-free days and delayed kidney recovery, highlighting the importance of early and sustained BP optimization. These findings support the use of age-appropriate BP targets, ideally informed by physiologic norms, to guide hemodynamic management in children at risk for or with AKI.

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Hemodynamic management for pediatric AKI relies primarily on extrapolated adult evidence, with limited direct pediatric data. The only pediatric RCT is the Goal-Directed Perfusion to Reduce Acute Kidney Injury after Paediatric Cardiac Surgery (GDP-AKIp) trial, which demonstrated that goal-directed perfusion maintaining indexed oxygen delivery ≥360 ml/min/m² during cardiopulmonary bypass reduced AKI from 42.2% to 28.1% in children undergoing cardiac surgery.[389] No pediatric-specific MAP targets exist. Elevated central venous pressure is associated with worse kidney function in children with congenital cardiac disease, with eGFR declining acutely as central venous pressure exceeds 6 mm Hg.[507] For vasopressor selection, pediatric septic shock guidelines recommend either epinephrine or norepinephrine as acceptable first-line agents,[508] though a recent propensity-matched study found norepinephrine was associated with lower mortality compared to epinephrine without clear kidney benefit.[509] Renal near-infrared spectroscopy is the most studied pediatric-specific noninvasive hemodynamic monitoring strategy, with multiple studies demonstrating that low intraoperative kidney tissue oxygenation predicts subsequent AKI in cardiac surgery patients.[510-512] Fluid management should avoid both hypovolemia and hype

3.12.2 Nutritional intervention in AKI

Practice Point 3.12.2.1.: In children with AKI or AKD, age-recommended protein targets can be used without protein restriction, and a minimum daily protein intake of 2.5 grams/kg should be maintained for children receiving CRRT.

Protein-energy malnutrition is common in critically ill children with AKI and is associated with adverse outcomes. Children receiving CRRT are at particularly high risk due to increased protein requirements for growth and additional protein losses through the extracorporeal circuit. Importantly, there is no evidence that protein intake at age-recommended protein levels delays kidney recovery in children with AKI, and restriction may contribute to negative nitrogen balance and worse outcomes. In a large retrospective study of 511 critically ill children, higher protein intake (≥80% of estimated needs) was not associated with delayed resolution of AKI, even after adjustment for severity of illness.[481]

Children receiving CRRT require even higher protein intake to counteract extracorporeal losses. A prospective study of 41 children receiving CRRT found that median protein delivery was 2.0 g/kg/day, with a substantial proportion failing to meet institutional protein goals of 2.5 g/kg/day. Children who received only enteral nutrition met protein goals only 13% of the time, while those on combined parenteral and enteral support met goals 60% of the time. Transitioning from parenteral to enteral nutrition was identified as a high-risk period for inadequate protein delivery.[513] These findings underscore the importance of maintaining at least 2.5 g/kg/day protein intake during CRRT, with consideration of supplemental parenteral nutrition or protein additives when enteral nutrition alone is insufficient.

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Practice Point 3.12.2.2: Supplement water-soluble vitamins routinely in children receiving CRRT.

Compared with adults, infants and young children have lower baseline reserves of many water-soluble vitamins and higher weight-adjusted metabolic requirements, increasing the risk of clinically significant deficiency during prolonged RRT. Observational data consistently demonstrate reductions in circulating concentrations of several water-soluble vitamins during CRRT, and deficiency may develop rapidly in the absence of supplementation.[514] Deficiency of water-soluble vitamins in critically ill children may contribute to impaired energy metabolism, lactic acidosis (thiamine deficiency), compromised immune and antioxidant function (vitamin C deficiency), neurologic dysfunction, cytopenias, and poor wound healing. Water-soluble vitamins have a wide therapeutic index, and the risk of toxicity with appropriate supplementation is low, as excess amounts are generally cleared.

Supplementation should be initiated at the start of CRRT and continued for the duration of therapy. Dosing should account for age, weight, nutritional intake (enteral or parenteral), and CRRT intensity. In some cases, higher-than-standard daily recommended doses may be required to offset extracorporeal losses, particularly in infants, small children, or those receiving high effluent rates.

3.12.3 Hepatorenal syndrome-associated AKI

Practice Point 3.12.3.1: It is reasonable to use terlipressin or norepinephrine for children with hepatorenal syndrome-associated AKI depending on the clinical care context and patient condition.

Pediatric hepatorenal syndrome physiology is similar to adult physiology but data on terlipressin in children are limited. However, retrospective data suggests that terlipressin may be effective in reversal of the hepatorenal pathology in children and is safe to use in children when administered as an infusion in the ICU, as intermittent dosing is associated with a higher incidence of gut ischemia.

Investigators retrospectively reviewed 16 pediatric participants with liver disease and AKI who received terlipressin in a single center in the UK.[515] Terlipressin administration led to a sustained increase in MAP and improvement in kidney parameters, particularly in participants with hepatorenal syndrome. Notably, terlipressin was associated with improvements in SCr and urine output, especially in children with hepatorenal syndrome (71.4% response rate at 48 hours). Adverse effects were reported as 3 instances of digital ischemia and feeding intolerance. Although 47.5% of participants died (28.5% in hepatorenal syndrome-associated AKI subgroup), mortality was attributed to underlying disease severity and not terlipressin use. Larger prospective trials are needed to confirm the efficacy and assess the role of terlipressin as a bridge to transplantation.

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Data on the role of norepinephrine as an alternative is absent for children. In children, evidence supporting vasoconstrictor therapy is sparse and largely derived from observational studies, small case series, and extrapolation from adult data. Nevertheless, the underlying pathophysiology of hepatorenal syndrome-associated AKI is similar across age groups, and potential benefits in kidney perfusion and function are biologically plausible. The Work Group judged that a cautious suggestion for use of terlipressin in children is appropriate, with emphasis on individualized decision-making and careful monitoring.

3.12.4 Theophylline use in neonates

Recommendation 3.12.4.1: We recommend a single dose of theophylline be given to neonates with severe perinatal asphyxia for the prevention of AKI (*1A*).

This recommendation places a high value on the reduction of AKI incidence in neonates with severe perinatal asphyxia with a single dose of theophylline, given the consistent short-term benefits and low risk of harm. However, the long-term kidney and neurodevelopmental safety of this intervention remains incompletely understood, and most studies to date were conducted in settings without therapeutic hypothermia. Therefore, centers using therapeutic hypothermia should consider the lack of interaction data when implementing this recommendation.

Key information

Balance of benefits and harms

Neonates with severe perinatal asphyxia have a high risk of AKI. Renal hypoperfusion and ischemia–reperfusion injury are central mechanisms in this population. Adenosine-mediated renal vasoconstriction contributes to reduced glomerular filtration in the early post-asphyxia period. Theophylline, a nonselective adenosine receptor antagonist, may attenuate this vasoconstriction and improve kidney blood flow when administered shortly after birth.

A single early dose of theophylline has been shown to reduce the incidence and severity of AKI in multiple RCTs. Meta-analysis of 5 RCTs comparing theophylline versus no theophylline in a total of 356 neonates with perinatal asphyxia showed that children treated with theophylline had a significantly lower incidence of AKI (OR: 0.24; 95% CI: 0.16–0.36). There was no difference in mortality (OR: 0.86; 95% CI: 0.46–1.62; Supplementary Table S62).[516]

Theophylline has a narrow therapeutic index and is associated with potential adverse effects, including cardiac arrhythmias, gastrointestinal disturbances, central nervous system irritability, and potential drug interactions. However, in published neonatal studies using a single prophylactic dose, serious adverse events have been uncommon, and most reported side effects were transient and self-limited. The risk of toxicity may be increased in preterm infants or in settings without appropriate dosing

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accuracy and monitoring capacity. However, long-term neurodevelopmental outcomes and safety in combination with therapeutic hypothermia remain understudied.

Certainty of evidence

There is high certainty of evidence that, for neonates with perinatal asphyxia, theophylline greatly reduces the risk of AKI but may not affect risk of death, however, with no evidence regarding serious adverse events among studies reporting AKI-related outcomes.[516]

Values and preferences

This recommendation places a high value on the prevention of AKI in neonates with severe perinatal asphyxia, given its association with increased morbidity, mortality, and long-term kidney risk. Healthcare professionals and caregivers are likely to prioritize short-term improvements in kidney function and fluid balance, particularly when the intervention is simple, inexpensive, and administered as a single dose. In settings with limited capacity for close cardiorespiratory monitoring, healthcare professionals may place greater weight on potential harms. Conversely, in settings where RRT is unavailable or difficult to provide, the value placed on AKI prevention may be particularly high.

Overall, the Work Group considered that most informed parents and healthcare professionals would favor administration of a single prophylactic dose of theophylline in neonates with severe perinatal asphyxia to reduce the risk of AKI, given the seriousness of the outcome and the generally low incidence of significant short-term adverse effects when appropriately dosed.

Resource use and costs

The administration of a single dose of intravenous theophylline is a low-cost intervention that requires minimal additional resources. Theophylline is available in both low- and high-resource settings and is inexpensive. No specialized equipment or monitoring beyond standard neonatal intensive care practices is needed. Because the intervention is administered as a one-time dose within the first hour of life, it does not add substantial labor or complexity to neonatal resuscitation or early postnatal care. Importantly, the potential to prevent AKI may reduce downstream healthcare utilization. As such, the use of prophylactic theophylline in eligible neonates is likely to be cost-saving or cost-neutral from a healthcare system perspective, although this has not been specifically studied.

Considerations for implementation

Successful implementation of this recommendation requires timely identification of neonates with severe perinatal asphyxia and early administration of theophylline. This necessitates clear local protocols for recognizing eligibility based on criteria such as Apgar scores, cord pH, base deficit, and need for resuscitation. Standardization of dosing and incorporation into neonatal resuscitation or post-resuscitation order sets may facilitate uptake. In settings where therapeutic hypothermia is used, additional caution is warranted,

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as data on the combined use of theophylline and cooling are limited. Even in resource-limited settings, implementation is feasible because the intervention involves a single dose and relies primarily on monitoring that is already standard for critically ill neonates.

Rationale

Neonates with severe perinatal asphyxia are at high risk for AKI due to renal hypoperfusion and ischemia–reperfusion injury. Clinical trials in neonates have demonstrated that a single prophylactic dose of theophylline administered shortly after birth reduces the incidence of AKI, lowers peak SCr, improves urine output, and may reduce the need for RRT.

Although the number of RCTs is limited and most studies are relatively small, the evidence consistently demonstrates kidney benefit with minimal harm. The magnitude of benefit is particularly meaningful in settings where access to RRT is limited or unavailable. The intervention is relatively simple, involving a single weight-based intravenous dose, which limits cumulative drug exposure and toxicity risk. Reported adverse effects in neonatal trials are generally mild and self-limited. Serious adverse events are rare when dosing is appropriate.

The Work Group judged that the benefits clearly outweigh the potential harms, supporting a Level 1 recommendation for use, with careful weight-based dosing and monitoring.

3.12.5 Use of nitric oxide in children

Recommendation 3.12.5.1: We recommend against routine use of inhaled nitric oxide to prevent cardiac surgery-associated AKI in children with low-complexity cardiac lesions and no signs of pulmonary hypertension or right ventricular dysfunction undergoing cardiopulmonary bypass (*1C*).

This recommendation applies specifically to children undergoing elective, low-complexity congenital heart surgery with cardiopulmonary bypass who do not have significant pulmonary hypertension or right ventricular dysfunction, in whom inhaled nitric oxide did not reduce AKI or RRT in a large RCT. The Work Group judged that routine use of inhaled nitric oxide in this setting is not recommended as it does not prevent AKI and may introduce risks, cost, and unnecessary complexity without clear clinical advantages. Inhaled nitric oxide may still be indicated for other cardiopulmonary indications in select populations.

Key information

Balance of benefits and harms

AKI is a significant complication following cardiopulmonary bypass in children.[517] Inhaled nitric oxide has been proposed to reduce the risk of AKI by enhancing renal perfusion; reducing ischemia–reperfusion injury, oxidative stress, and hemolysis; preserving microvascular integrity; and attenuating inflammation. However,

there is no evidence supporting the clinical efficacy of inhaled nitric oxide for preventing AKI in low-complexity pediatric cardiac surgeries.

A systematic review of 6 RCTs among children undergoing surgery with cardiopulmonary bypass found that inhaled nitric oxide versus placebo had no effect on mortality (5 trials, 1686 participants; RR: 1.11; 95% CI: 0.53–2.34), development of AKI (1 trial, 1364 participants; RR: 1.16; 95% CI: 0.88–1.53), or use of RRT (1 trial, 1364 participants; RR: 0.94; 95% CI: 0.71–1.25; Supplementary Table S63).[518-524]

Only one large, multicenter RCT has examined AKI in infants undergoing congenital heart surgery and nitric oxide use. The Nitric Oxide During Cardiopulmonary Bypass to Improve Recovery in Infants With Congenital Heart Defects trial (NITRIC) was a large, multicenter, double-blind RCT conducted across 6 pediatric cardiac centers in Australia, New Zealand, and the Netherlands.[524] The trial enrolled 1371 children under 2 years of age undergoing elective, low-complexity congenital heart surgery with cardiopulmonary bypass, comparing inhaled nitric oxide at 20 ppm delivered into the cardiopulmonary bypass oxygenator with standard care. The primary outcome (ventilator-free days at 28 days) did not differ significantly between groups (median 26.6 days vs. 26.4 days; *P*=0.92). There were no significant differences in secondary outcomes, including the composite of low cardiac output syndrome, extracorporeal life support, or death by day 28. Rates of postoperative AKI and RRT were also not significantly different. These findings suggest that inhaled nitric oxide administration during cardiopulmonary bypass does not improve clinical outcomes or reduce AKI incidence in infants undergoing low-complexity congenital heart surgery.

In one small RCT of 16 children undergoing cardiopulmonary bypass surgery, inhaled nitric oxide resulted in less loop diuretic use in the intervention arm (1.63 ml ± 0.9 vs. 3.25 ml ± 1.0 total within 48 hours; $p<0.05$) and less positive postoperative fluid balance (187±122 vs. 317±271).[518]

Some evidence also suggests that inhaled nitric oxide may increase the risk of AKI, particularly in children with acute lung injury or acute respiratory distress syndrome. A systematic review and meta-analysis of 10 RCTs involving 1363 participants found that inhaled nitric oxide increased AKI risk (RR: 1.40; 95% CI: 1.06–1.83; p=0.02), with a dose-dependent effect, as higher cumulative doses of inhaled nitric oxide significantly increased AKI risk (RR: 1.52; p=0.004). However, this harm was specific to participants with acute respiratory distress syndrome and was not observed in non-acute respiratory distress syndrome populations.[525] A 2016 Cochrane review, which examined 4 studies, found that abnormal kidney function was more frequent in the inhaled nitric oxide group compared to the control group, with a relative risk of 1.59 (95% CI: 1.17–2.16, $I^2 = 0\%$).[526]

While inhaled nitric oxide is generally well tolerated when used short-term, there are potential harms and adverse effects, including methemoglobinemia, nitrogen dioxide

toxicity, rebound pulmonary hypertension, systemic hypotension, platelet dysfunction, and bleeding. These harms may negate any benefit when used for AKI prevention in the absence of pulmonary hypertension.

The Work Group judged that the balance of benefits and harms of inhaled nitric oxide for the specific purpose of AKI prevention is context-dependent. In children with clear pulmonary hypertension or right ventricular dysfunction, inhaled nitric oxide may provide cardiopulmonary benefit that justifies potential risks, with kidney protection as a possible secondary advantage. However, when used solely for kidney protection in hemodynamically stable children without pulmonary vascular disease, the anticipated benefits are uncertain.

Certainty of evidence

There is low certainty of evidence that in children undergoing cardiopulmonary bypass inhaled nitric oxide during anesthesia does not affect the risk of AKI, RRT, death, or length of stay, with imprecise estimates of serious adverse events. The certainty of evidence was downgraded for imprecision and sparseness of data.[518-524]

Values and preferences

Most families and healthcare professionals place a high value on avoiding unnecessary interventions in children undergoing low-complexity cardiac surgery, particularly when the anticipated benefit is uncertain and the therapy involves additional cost, monitoring, and potential risks. Parents and caregivers are likely to value avoidance of unnecessary medications, potential side effects, and additional interventions. The principle of minimizing nonessential therapies in children is often strongly supported in shared decision-making discussions.

Many healthcare professionals would prioritize minimizing exposure to therapies that do not demonstrate clear and consistent benefit on patient-important outcomes. Some variability in preferences may exist, and some healthcare professionals may favor broader use of inhaled nitric oxide, based on institutional experience, physiologic rationale, or perceived safety. However, in the absence of compelling evidence of benefit in children at low risk, most informed healthcare professionals would likely favor a conservative approach.

Resource use and costs

Inhaled nitric oxide is a high-cost intervention that requires specialized delivery systems, continuous monitoring, and trained personnel for safe administration. The infrastructure needed to deliver inhaled nitric oxide, whether integrated into the cardiopulmonary bypass circuit or postoperatively in the ICU, may not be readily available in all settings, particularly in low- and middle-resource settings. In the absence of demonstrated benefit for AKI prevention in low-risk pediatric cardiac surgical populations, routine use of inhaled nitric oxide represents a poor allocation of resources.

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Its continued use in this context may divert financial and staffing capacity from interventions with stronger evidence of clinical efficacy.

Considerations for implementation

This recommendation applies specifically to children undergoing elective, low-complexity congenital heart surgery with cardiopulmonary bypass, such as ventricular septal defect or atrial septal defect repairs, who do not have significant pulmonary hypertension or ventricular dysfunction. In these children, inhaled nitric oxide should not be used solely for the purpose of AKI prevention. However, inhaled nitric oxide may still be indicated for other clinical reasons. It is important that healthcare professionals do not generalize this recommendation to higher-risk populations, such as those with single-ventricle physiology, complex cyanotic heart lesions, or preexisting pulmonary vascular disease, where the benefit-risk profile may differ.

Rationale

Cardiac surgery–associated AKI is related to ischemia–reperfusion injury, inflammation, hemolysis, hemodynamic instability, and venous congestion during and after cardiopulmonary bypass. Inhaled nitric oxide has been proposed as a preventive strategy based on its potential to improve right ventricular performance, enhance pulmonary vascular function, mitigate hemolysis-mediated nitric oxide depletion, and attenuate oxidative stress.

Available clinical studies evaluating inhaled nitric oxide for AKI prevention in pediatric cardiac surgery are limited, heterogeneous, and largely conducted in mixed or higher-risk populations. Evidence does not consistently demonstrate a meaningful reduction in patient-important outcomes such as need for RRT, prolonged ICU stay, or mortality. Furthermore, inhaled nitric oxide therapy carries potential risks and burdens, including methemoglobinemia, nitrogen dioxide exposure, rebound pulmonary hypertension with abrupt discontinuation, platelet inhibition, and potential contribution to postoperative bleeding. Although these harms are generally uncommon and manageable, their relevance increases when expected benefit is small or uncertain.

Accordingly, the recommendation against routine use reflects the low baseline risk of severe AKI, lack of evidence of clinically meaningful benefit, and the additional risks and resource implications associated with inhaled nitric oxide therapy in this setting.

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CHAPTER 4. DRUG- AND NEPHROTOXIN-ASSOCIATED AKI

Drug-associated kidney disease is a significant problem in community- and hospital-based care. Approximately one-fourth of all medications used in hospitals can cause injury to the kidneys, and these substances contribute to approximately one-fourth of all AKI episodes. There are multiple mechanisms by which drugs can cause AKI or AKD, although not all involve structural damage to the renal tubules or other parenchymal components. Medications like renin-angiotensin system inhibitors (RASi) and sodium glucose transporter 2 inhibitors (SGLT2i) may cause a rise in SCr through hemodynamic effects on GFR but confer proven and clinically significant outcome-modifying benefits for high-risk patient populations, including those with heart failure, CKD, and diabetes.

Iodinated contrast agents have long been associated with AKI, but their direct effect on kidney function and nephrotoxicity remains debated. Meanwhile, the types of contrast media and clinical practices to increase the safety of radiocontrast exposure have changed considerably over time.

This chapter provides guidance on drug stewardship and contrast use in people at risk of or with AKI or AKD. Throughout this chapter, the terms "nephrotoxic" and "nephrotoxicity" are used only to describe medications or chemicals when they cause structural damage to the kidneys. This is intended to makes clear a distinction between drug effects on GFR due to alterations in kidney hemodynamics, from those that induce structural kidney damage.

4.1. Categorization and classification of medications associated with AKI

Practice Point 4.1.1: Drugs that may contribute to AKI can be classified into one of 4 categories based on kidney function and damage biomarkers assessed at the time of exposure (Figure 11).

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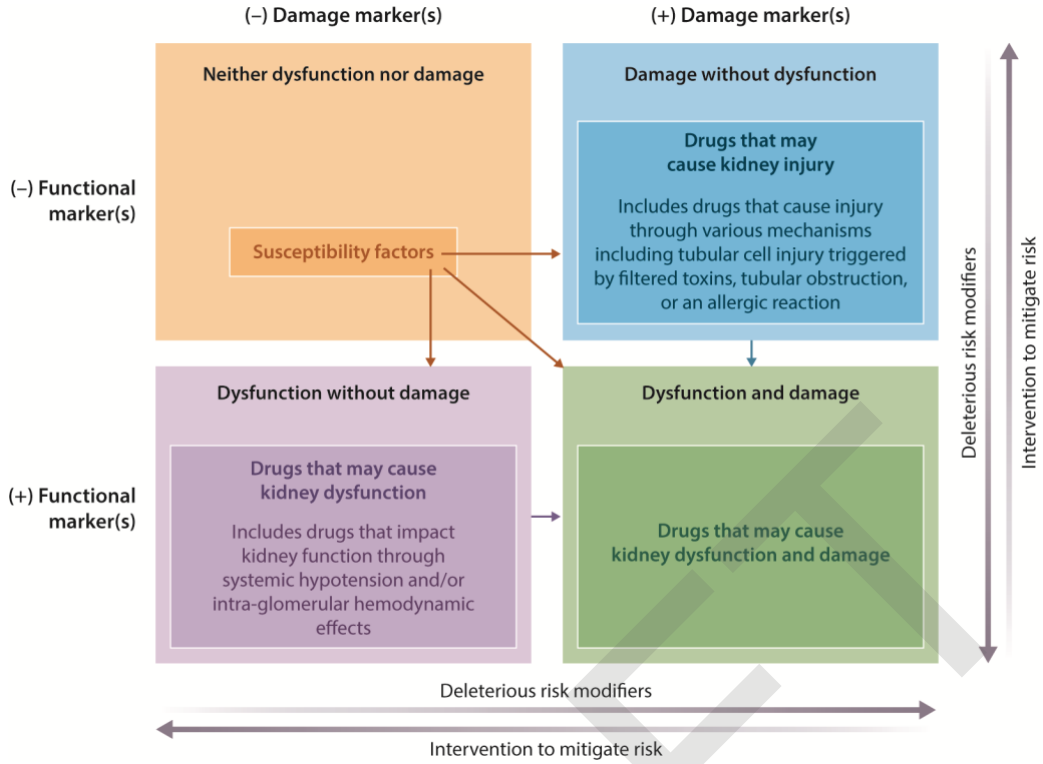
(–) Damage marker(s)
(+) Damage marker(s)
Neither dysfunction nor damage
Damage without dysfunction
Drugs that may cause kidney injury
Includes drugs that cause injury through various mechanisms including tubular cell injury triggered by filtered toxins, tubular obstruction, or an allergic reaction
(–) Functional marker(s)
Susceptibility factors
Dysfunction without damage
Dysfunction and damage
Drugs that may cause kidney dysfunction
Includes drugs that impact kidney function through systemic hypotension and/or intra-glomerular hemodynamic effects
(+) Functional marker(s)
Drugs that may cause kidney dysfunction and damage
Deleterious risk modifiers
Intervention to mitigate risk
Deleterious risk modifiers
Intervention to mitigate risk

Figure 11 | Classifying drugs that potentially cause AKI.[527] Iterative classification of agents that have potential to cause kidney dysfunction/abnormal kidney function or kidney injury or both. Functional and injury biomarkers have a role in distinguishing among the different pathophysiological processes. Examples of deleterious risk modifiers are duration of therapy, drug burden, hypotension, and pharmaco/pharmacodynamic interactions. Examples of interventions to mitigate risk are daily dynamic prescribing, kidney monitoring, and patient and provider education. Susceptibility factors include those listed in Table 14 in Chapter 2. Any final impact depends on underlying susceptibility, associated risk factors, clinical context, drug management, and modifying factors. Examples of drugs that correspond to the relevant categories above include trimethoprim, cimetidine (neither dysfunction nor damage); angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers (dysfunction without damage); aminoglycoside, acyclovir, vascular endothelial growth factor antagonists (damage without dysfunction); and nonsteroidal anti-inflammatory drugs (dysfunction and damage). AKI, acute kidney injury. Adapted from Ostermann et al. 2020.[528]

The 4 categories presented in Figure 11 classify drugs as those that affect SCr concentration but do not cause abnormal kidney function (e.g., decline in GFR, dysfunction) or structural damage, drugs that may cause damage but not dysfunction, may cause dysfunction but not damage, and drugs that may cause both damage and dysfunction.[527] The mechanisms of toxicity vary. They can also be further categorized by assessing whether they are predictable based on the pharmacology of the drug and dose dependency, or unpredictable not based on the pharmacology of the drug and not dose-dependent. Further, the processes are dynamic. For instance, initial tubular damage without dysfunction can later lead to abnormal kidney function.

a) *Neither dysfunction nor damage:* Drugs that are known to interfere with the tubular secretion of creatinine, interfere with creatinine assay measurements, or increase

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creatinine production without damage to the kidney's glomeruli, tubules, or interstitium can cause a rise in SCr without underlying damage or dysfunction. The resulting clinical condition has been termed pseudo-AKI in the literature (Table 26).

Table 26 | List of drug/drug classes associated with pseudo-AKI and their possible mechanisms.

Dug/drug classes	Mechanisms
Antibiotics/antivirals:[a] Trimethoprim[b], pyrimethamine, cobicistat, dolutegravir Antiarrhythmics: Dronedarone Gastrointestinal agents: Cimetidine Antineoplastics: Tyrosine kinase inhibitors (e.g., imatinib, bosutinib, sorafenib, sunitinib, crizotinib, gefitinib, and pazopanib) Poly-ADP-ribose polymerase inhibitors (e.g., olaparib, niraparib talazoparib) Cyclin-dependent kinase 4/6 inhibitors (e.g., palbociclib, abemaciclib, ribociclib) Anaplastic lymphoma kinase inhibitors (e.g., crizotinib, ceritinib, alectinib, brigatinib, lorlatinib) Others: Probenecid	Competing with and decreasing proximal tubule creatinine secretion in a dose-dependent manner, mediated via the inhibition of drug efflux transporters such as organic cation transporter
Creatine supplements (both short-term and long-term)	Increasing the precursor of creatinine
Corticosteroids	Increasing catabolic state is associated with the release of creatine from muscle, spontaneously converted to creatinine Some formulations of dexamethasone may contain creatinine as a buffer excipient.
Azasetron	Some formulations may contain creatinine as a buffer excipient.
Fenofibrate	Increasing the metabolic production of creatinine
Cephalosporins (e.g., cephalothin, cefazolin, cephalexin, cefoxitin, cefaclor, cephradine), clavulanic acid	Interfering with the analytical measurement of creatinine (Jaffe method)
5-Flucytosine	Interfering with the analytical measurement of creatinine (Ektachem enzymatic system)
Calcitriol and alfacalcidol	Unknown

[a]Pseudo-AKI via inhibiting organic anion transporters 1 and 3 in proximal tubule has also been reported with antibiotic combinations such as piperacillin/tazobactam or vancomycin plus piperacillin/tazobactam.[529, 530] Nevertheless, interstitial nephritis due to piperacillin/tazobactam has been documented in the literature.[531, 532] Thus, it seems prudent not to place piperacillin/tazobactam into the "neither dysfunction nor damage" category. [b]Sulfamethoxazole/trimethoprim should be discriminated from trimethoprim alone and viewed as an independent agent because of described interstitial nephritis or crystal nephropathy cases induced by sulfamethoxazole/trimethoprim.[533]

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Therefore, sulfamethoxazole/trimethoprim may not match the "neither dysfunction nor damage" category. AKI, acute kidney injury. Reproduced from Karimzadeh et al. 2023.[527]

b) *Damage without dysfunction:* Many drugs commonly referred to as nephrotoxic can fit within this category. There are multiple mechanisms of kidney damage (e.g., vascular/glomerular damage, tubular injury, crystal formation, interstitial nephritis etc.; Table 27). As kidney function is not affected, SCr will not change. Reliance on SCr alone as a marker of AKI means that these events may go undetected until they progress and affect kidney function (and SCr) as well.

Table 27 | Examples of mechanisms and nephrotoxins that cause damage (structure changes to the kidneys) without dysfunction (reduction in GFR)

Mechanism	Examples
Acute tubular injury	Aminoglycosides, amphotericin, colistin, vancomycin, nonsteroidal anti-inflammatory drugs
Acute interstitial nephritis	Antibiotics, proton pump inhibitors
Glomerular disorder	Hydralazine
Tubular obstruction	Acyclovir
Vascular damage	Mitomcyin, tacrolimus

GFR, glomerular filtration rate

c) *Dysfunction without damage:* This category refers to the effects of drugs through systematic hypoperfusion and/or a decline in the intraglomerular pressure that lead to a decrease in GFR and increase in SCr without structural damage. Examples are ACEi, ARBs, and SGLT2i. Notably, the acute reduction in GFR can be anticipated and desirable as in the case of ACEi, ARB, or SGLT2i use for renoprotection of people with CKD and proteinuria.

d) *Dysfunction with damage:* These include many drugs exerting more than one effect of structural damage or prolonged damage leading to reduced GFR. Examples include nonsteroidal anti-inflammatory drugs (NSAIDs), calcineurin inhibitors, aminoglycosides, and amphotericin B.

Of relevance to clinical decision making, some classes of drugs can cause an acute reduction in GFR but confer important long-term kidney and cardiovascular health benefits (e.g., ACEi, ARB, and SGLT2i). This is particularly relevant to management of people with heart failure and CKD, who may have a rise in SCr meeting criteria for AKI or AKD following initiation or dose escalation of such medications. Small declines in eGFR in such situations are expected and have been associated with better long-term outcomes. Similarly, diuretics for acute heart failure may cause hemoconcentration and changes in SCr concentration meeting AKI criteria. However, achieving decongestion in this situation is crucial for improving both short- and long-term outcomes.

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4.2. Kidney protective strategies

Recommendation 4.2.1: For children or adults with or at risk of AKI, we recommend drug and nephrotoxin stewardship using a multimodal approach (*1C*).

This recommendation places high value on patient safety by seeking to minimize the risk of adverse reactions to drugs eliminated by the kidney and by reducing the incidence and severity of AKI related to drug exposures. It emphasizes the principles of drug stewardship which refers to the use of multiple strategies to promote responsible, effective, and safe use of medicines to ensure they are initiated when needed at the right dose, monitored and dose adjusted as needed to prevent or minimize harm, and are discontinued when no longer beneficial to a person's health. A clinical pharmacist often leads this form of multimodal stewardship, but other healthcare professionals may take on this role. This recommendation places a lower value on the additional resource use associated with the multimodal drug stewardship. Although the certainty of evidence for a multimodal strategy is low (or very low), the Work Group felt that a Level 1 recommendation was warranted given the potential for harm and cost reduction in applicable populations.

Key information

Balance of benefits and harms

Drug and nephrotoxin stewardship strategies offer the benefits of safer and more effective use of medications. Potential harms include avoidance of otherwise effective medications for the treatment of acute and chronic illnesses due to fears of causing AKI. Other challenges are differences in financial costs between different drugs with different nephrotoxic potential. The balance between risk and benefit comes into consideration when prescribing potentially nephrotoxic medications or medications cleared by the kidney and deciding when benefits of treatment exceed the risk of causing or worsening AKI, and whether it is appropriate to initiate, dose-adjust, or discontinue such medications. Drug stewardship can help support these decisions by improving recognition of potential medication harms and involving multidisciplinary healthcare professionals in medication stewardship decisions to balance protection of kidney health while ensuring adequate treatment of underlying diseases with acceptable levels of AKI risk.

Vancomycin has been the focus of several studies. A review of 9 studies (1 RCT and 8 nonrandomized controlled studies), including a total of 1973 adults showed that vancomycin administered via continuous infusion was associated with a significantly lower risk of AKI (OR: 0.47; 95% CI: 0.34–0.64) compared to intermittent dosing but there was no difference in mortality (Supplementary Table S64).[534-536]

A systematic review of 12 nonrandomized controlled studies including 7548 adults concluded that vancomycin dosing based on AUC was associated with a significantly lower risk of AKI development compared to trough-only guided dosing (RR: 0.68; 95% CI: 0.59–0.77; Supplementary Table S65).[537]

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Based on data of 9 RCTs, including 18,355 adults, the use of CDSS with therapeutic vancomycin monitoring compared with not using CDSS was not associated with prevention of AKI (RR: 1.11; 95% CI: 0.99–1.24; Supplementary Table S66).[151]

Data from 35 studies (1 RCT, 15 nonrandomized studies, and 19 pre-post reports), including 2 studies in children, concluded that pharmacist interventions for vancomycin monitoring reduced the risk of AKI (RR: 0.59; 95% CI: 0.48–0.72; Supplementary Table S67).[538, 539] The 2 studies in children provided a consistent, but highly imprecise estimate of risk of AKI (RR: 0.30; 95% CI: 0.04–2.34).[540, 541]

Other studies evaluated monitoring of beta-lactam and other antibiotics. A review of 3 studies in adults (1 RCT and 2 nonrandomized controlled studies) concluded that therapeutic drug monitoring of beta-lactam antibiotics (in 2 studies[542, 543]) or of various antibiotics (vancomycin, ciprofloxacin, meropenem, and ceftriaxone (1 study[155]) did not affect the development of AKI (Supplementary Table S68). A single RCT compared conventional versus prolonged infusion of meropenem in 102 neonates and showed a lower risk of AKI with more prolonged infusion (RR: 0.25; 95% CI:0.07–0.83; Supplementary Table S69).[544]

The role of therapeutic drug monitoring to prevent aminoglycoside nephrotoxicity has only been investigated in observational studies. A meta-analysis of 5 observational studies involving 615 participants were reported for gentamicin, and 2 observational studies involving 159 participants were identified for amikacin. The analysis concluded that target trough concentrations (Cmin) <2 mg/l for gentamicin and Cmin <10 mg/l for amikacin may reduce the risk of nephrotoxicity.[545]

The role of pharmacist-led interventions in prevention of AKI outcomes has been investigated in children and adults. As mentioned earlier, pharmacist interventions based on vancomycin monitoring reduced the risk of AKI in children and adults.[538, 539] A single RCT in 150 adults in the ICU compared the involvement of a clinical pharmacist (i.e., drug selection, drug administration routes, drug dose adjustment, drug-drug interactions, drug-food interactions, drug side effect management, and drug incompatibility) with no interventions by a clinical pharmacist and showed a lower risk of drug induced AKI in participants randomized to the intervention group (RR: 0.39; 95% CI: 0.19–0.79; Supplementary Table S70).[546]

Overall, these studies demonstrate that drug stewardship including therapeutic drug monitoring and informed interventions can prevent drug induced AKI. However, additional resources (laboratory, experts, costs) are needed. Also, in some situations, administration of nephrotoxic drugs may be needed to treat the underlying illness. Importantly, drug stewardship is only 1 strategy to protect kidney health and may not be sufficient to prevent multi-factorial AKI.

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Certainty of evidence

There is moderate certainty of evidence that continuous versus intermittent infusion of vancomycin reduces the risk of AKI in adults but does not affect mortality. The certainty was downgraded for some methodological limitations and sparseness of data.[534-536] There were no eligible studies comparing vancomycin infusion in children.

There is low certainty of evidence that AUC dosing of vancomycin versus trough-based dosing reduces the risk of AKI in adults but does not affect mortality (with very low certainty of evidence). The certainty was downgraded for methodological limitations of observational studies and, for mortality, sparseness of data.[537] There were no eligible studies comparing vancomycin infusion in children.

There is low certainty of evidence regarding CDSS interventions (including therapeutic monitoring) for vancomycin in adults. The overall certainty of evidence was based on prioritizing incident AKI, but there is moderate certainty of evidence for a possible increase in RRT and mostly moderate to high certainty of evidence for mortality and other sequelae of AKI.[151, 547] The certainty of evidence for incident AKI was reduced due to sparseness of data (adequately powered single study). The certainty of evidence for RRT was downgraded for imprecision. There were no eligible studies of CDSS interventions for vancomycin in children.

For adults with AKI, with low certainty of evidence, pharmacist involvement in vancomycin dosing is associated with reduced risk of death and incident AKI. The certainty of evidence was downgraded for methodological quality (almost all data come from observational studies).[538, 539] From a subset of these studies, there is very low certainty of evidence of a similar effect in children; however, the certainty of evidence for children was also downgraded for inconsistency and imprecision.

Antibiotic monitoring (other than for vancomycin) in adults with AKI has low certainty of evidence of no effect on AKI.[155, 542, 543] The certainty of evidence was downgraded for sparseness (for monitoring of specific antibiotics), methodological limitations of the studies, and imprecision. There were no eligible studies of antibiotic monitoring overall in children.

There is very low certainty of evidence that slow infusion of meropenem in neonates reduces the risk of all-cause mortality and AKI compared with conventional infusion.[544] The certainty of evidence was downgraded for methodological limitations and sparseness of evidence from a single study.

There is low certainty that pharmacist monitoring of all drugs in adults in the ICU may reduce the risk of AKI. The certainty was downgraded for some methodological limitations and sparseness of data.[546] There were no eligible studies of pharmacist monitoring of all drugs in children.

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Values and preferences

Drug and nephrotoxin stewardship are predicated on the understanding that there are no specific treatments available for AKI and that patients and healthcare professionals prefer prevention. This recommendation values diligent monitoring through stewardship efforts to avoid thinking that drug-related kidney disease is an accepted risk for all. It is a preference towards an active approach to patient-centered care designed to avoid medication-related harm.

Resource use and costs

Available resources are an important consideration in the selection of stewardship strategies and require that institutions commit resources to medication safety (Table 28).[548] Resources to accomplish drug and nephrotoxin stewardship include support for healthcare professionals committed and assigned to providing the set of coordinated patient care management strategies. When deciding the cost of personnel, it is important to consider the immediate and long-term cost of drug-related acute kidney diseases. The additional costs of dedicating personnel and resources to support drug stewardship could be offset by reduced total drug costs, shorter lengths of stay in ICU and hospital, and improved downstream health status by avoiding AKI.[549]

Considerations for implementation

Drug and nephrotoxin stewardship encompass a set of coordinated patient care management strategies to improve the appropriate and safe use of drugs for the kidneys. Medication safety requires the provision of appropriate drug dosing (avoidance of overdosing or underdosing) to people at risk or with AKI and appropriate monitoring for kidney dysfunction or damage. Examples of the elements of multimodal drug and nephrotoxin stewardship are provided in Table 28. Successful implementation requires strategic planning, multidisciplinary collaboration, effective education, technological support, and ongoing evaluation.

Table 28 | Multimodal approach to drug and nephrotoxin stewardship

Objective	Examples of fundamental approaches
Appropriate drug dosing to prevent adverse drug reactions	• Monitor changes/trends in kidney function and select appropriate dosing for drugs eliminated by the kidney. • Therapeutic drug monitoring of drugs eliminated by the kidney with narrow therapeutic indices.
Prevent AKI, AKD, CKD development or progression, promote resolution of AKI	• Monitor pharmacokinetic and pharmacodynamic drug-drug interactions with potential for nephrotoxicity including a nephrotoxic burden assessment. • Therapeutic drug monitoring of nephrotoxic drugs with narrow therapeutic indices. • Where available, use pharmacologic evidence-based prevention strategies for specific drugs, for fluid therapy to prevent crystalline nephropathies.

AKI, acute kidney injury; AKD, acute kidney disease; CKD, chronic kidney disease

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Rationale

There are multiple approaches to prevent the development or progression of drug- or nephrotoxin-related AKD or adverse events from drugs eliminated by the kidney. As no single strategy has demonstrated superiority over others, the best option for surveillance and mitigation of drug related adverse events in people of all ages is to employ a set of multiple, coordinated management strategies (multimodal approach) in people at risk for these complications.[550] Selecting a less nephrotoxic drug in people at-risk for AKI, reducing nephrotoxin burden, or applying dose reduction/trough reduction to minimize exposure as part of a stewardship strategy can result in improved clinical outcomes and reduce drug use and related costs. Therapeutic drug monitoring, and surveillance for drug-drug interactions have also been included in effective interventions. Table 31 of the *KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of CKD* provides suggestions for non-nephrotoxic alternatives to nephrotoxic drugs.[17] These alternatives can also be applied to people with AKI or AKD. The impact of medication burden and the principles of medication reviews and reconciliation to ensure medication safety that are outlined in Figure 46 of the *KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of CKD* also apply to people with AKI or AKD.[17] However, in the context of AKI and potentially fluctuating GFR, closer monitoring and more frequent adjustments may be required.

Practice Point 4.2.1: Strategies to manage drug-related acute kidney disease include:

d) discontinuation of offending nephrotoxic agents known to cause kidney damage, if possible;

e) provision of a therapeutic equivalent alternative that is less nephrotoxic, if available and necessary;

f) reduction in dose if drug continuation is necessary for those drugs with a dose dependent direct nephrotoxic effect.

An assessment of risk versus benefit is required when determining whether to discontinue or continue medications in situations where ongoing exposure can possibly lead to development or progression of AKI. This decision should be made with consideration of the availability of therapeutically equivalent, alternative agents, and the relative effectiveness of alternative agents for the clinical condition the drug is being prescribed for. Another factor to consider is whether to opt for dose reduction versus discontinuation which may be affected by the mechanism of nephrotoxicity. If toxicity is dose dependent, a dose reduction may be beneficial as opposed to dose-independent toxicity (e.g.,, in drug-induced acute interstitial nephritis) where drug discontinuation is required.

Practice Point 4.2.2: Therapeutic drug monitoring is a component of multimodal stewardship that involves serial assessments of drug concentrations in children and adults receiving potentially nephrotoxic drugs, drugs excreted by the kidneys, and drugs with narrow therapeutic margins or low therapeutic indices.

Therapeutic drug monitoring is the clinical practice of measuring plasma concentrations of specific drugs at designated intervals to optimize drug dosing. It can be

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used to assess drugs with narrow therapeutic indices that cause nephrotoxicity, are eliminated by the kidneys, or both. (Table 29).[551, 552] Therapeutic drug monitoring is appropriate for potentially nephrotoxic drugs that require vigilant monitoring to prevent AKI development or progression.[553] An appropriately trained member of the care team or a CDSS is needed to interpret therapeutic drug monitoring results and make dosage adjustments.[551] Follow-up monitoring after drug discontinuation may be needed if supratherapeutic drug concentrations are observed.[554] Importantly, there is a strong association between nonadherence to therapeutic drug monitoring guidelines for antibiotics and the development of nephrotoxicity.[555] Therapeutic drug monitoring should also be considered for classes of medications that depend on renal clearance and may accumulate in case of reduced kidney function (Table 29).

Table 29 | Therapeutic drug monitoring for drugs that are potentially nephrotoxic or excreted by the kidney

Drug class	Examples	Characteristic(s)
Antibiotics	Amikacin, Gentamicin Tobramycin	Both excreted by the kidney and potentially nephrotoxic
	Vancomycin	Both excreted by the kidney and potentially nephrotoxic
Antineoplastics	Methotrexate	Both excreted by the kidney and potentially nephrotoxic
Antiepileptics	Phenobarbital	Excreted by the kidney
Antifungals	Voriconazole	Excreted by the kidney
Cardiac drugs	Lidocaine	Excreted by the kidney
	Digoxin	Excreted by the kidney
Immunosuppressants	Cyclosporine, Tacrolimus Sirolimus	Both excreted by the kidney and potentially nephrotoxic
Psychiatric drugs	Lithium	Both excreted by the kidney and potentially nephrotoxic

Practice Point 4.2.3: Surveillance for pharmacokinetic and pharmacodynamic drug-drug interactions that increase the risk of AKI is a component of multimodal stewardship.

There are several pharmacokinetic drug-drug interactions that potentiate the likelihood of developing AKI (Table 30).[556] Some of these interactions can be avoided by selecting alternative drugs that do not alter the metabolism of another drug (i.e. selecting azithromycin instead of erythromycin and clarithromycin to reduce the risk of rhabdomyolysis when coadministration with a statin is necessary).

Also, several pharmacodynamic drug combinations can result in an increased risk of developing AKI, for instance the coadministration of NSAIDs, diuretics, and RASi.[556, 557] While it may be necessary to continue coadministration of drugs such as ACEi and diuretics for people with congestive heart failure, coadministration of NSAIDS can often be avoided.

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The likelihood of developing AKI increases depending on the number of nephrotoxin exposures for an individual. Nephrotoxic burden refers to the cumulative or aggregate exposure to nephrotoxins, with consideration to the nephrotoxic potential for each drug, evaluated within a relevant time frame.[550, 558-560] Specifically, each additional nephrotoxin has been estimated to contribute to a 1.2–1.8-fold increase in odds of AKI per drug in children and a 1.2–3.2-fold increase in odds per drug in adults.[561] Calculations for assessing nephrotoxic burden have been proposed.[558, 562, 563] Surveillance for the nephrotoxic burden of ≥3 drugs with notification to the healthcare professional using CDSS has been shown to reduce AKI incidence and severity in children.[420, 564, 565]

Table 30 | Examples of pharmacokinetic and pharmacodynamic drug-drug interactions associated with risk of kidney damage or dysfunction[556]

Drug-drug interaction type	Interacting drug/drug class	Proposed mechanism increasing the risk of kidney damage or dysfunction
Pharmacodynamic	NSAIDs and diuretics	Decrease in prostaglandin synthesis with NSAID administration causing vasoconstriction of the afferent arteriole and a decrease in effective blood volume with diuretics
	NSAIDS and diuretic plus RASi "triple whammy"	Cumulative pharmacodynamic effect from the administration of each drug-decrease in prostaglandin synthesis with NSAID administration causing vasoconstriction of the afferent arteriole and a decrease in effective blood volume with diuretics exacerbated by the efferent arteriolar vasodilation caused by the RASi.
Pharmacokinetic	Calcium channel blockers and clarithromycin/erythromycin	Cytochrome P459 3A4 (CYP3A4) enzyme inhibition with clarithromycin causing elevated concentrations of calcium channel blockers that are metabolized by CYP3A4 leading to systemic hypotension and indirect abnormal kidney function. Drug-drug interactions could also be applicable to other CYP3A4 isoenzyme inhibitors.
	Statins and calcium channel blockers	Certain calcium channel blockers (amlodipine, diltiazem, felodipine, nicardipine, nifedipine, and verapamil) inhibit CYP450 3A4 metabolism of statins leading to increased statin concentration, rhabdomyolysis, and AKI.
	Statins and clarithromycin/erythromycin	Certain statins (simvastatin, lovastatin, and atorvastatin) are metabolized by CYP3A4 isoenzyme and inhibition with macrolides causes

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		increased serum statin concentrations leading to rhabdomyolysis and AKI.

AKI, acute kidney injury; NSAID, nonsteroidal anti-inflammatory drugs; RASi, renin-angiotensin-aldosterone inhibitor

Practice Point 4.2.4: Intravenous hydration strategies may be used for the prevention of drug-induced crystalline nephropathies as part of multimodal stewardship.

Intravenous crystalloid fluid administration is commonly used for the prevention of AKI when drugs are indicated that cause crystalline nephropathies.[566, 567] However, there is no consensus on optimal hydration protocols. Typical prescriptions in adults include administration of 1–2 l of intravenous isotonic crystalloids pre- and post-medication administration. Table 31 describes strategies for prevention of drug-induced crystalline nephropathies, including isotonic fluids and urinary alkalinization.[568]

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Table 31 | Drug-induced crystalline nephropathies

Culprit medication	Clinical kidney syndromes	Histologic findings	Preventive and therapeutic strategies[a]
Methotrexate	Crystalluria, AKI, and CKD	Crystals form annular structures consisting of small needle-shaped crystals that stain yellow, golden, or brown on H&E stain, weak rim staining on PAS, black staining on JS, and positively birefringent on polarization	IVFs before/during drug, alkalinize urine, adjust drug dose for kidney function; folinic acid; glucarbidase (<60 h after methotrexate); high-flux HD in certain circumstances
Sulfadiazine, sulfamethoxazole	Crystalluria, AKI, CKD, and nephrolithiasis	Interstitial fibrosis with mild mononuclear inflammation observed in absence of sulfa crystals within tubules or interstitium	Alkalinize urine, adjust dose for kidney function, assure euvolemia before drug exposure
Indinavir, atazanavir, darunavir	Crystalluria, AKI, CKD, and nephrolithiasis	Translucent, needle-shaped indinavir, atazanavir, or darunavir crystals within tubules with an associated monocytic infiltrate and giant-cell reaction	No role for urine acidification, assure euvolemia during drug therapy; switch to different medication
Acyclovir	Crystalluria, AKI, and CKD	Needle-shaped crystals within tubules +/−peritubular inflammation and positively birefringent on polarization	Avoid rapid iv bolus, adjust drug dose for kidney function, assure euvolemia during drug therapy
Ciprofloxacin, levofloxacin	Crystalluria and AKI	Needle-shaped crystals within tubules and strongly birefringent with polarization	Assure euvolemia during drug therapy and avoid alkaline urine (if possible)
iv ascorbic acid, orlistat (by causing enteric hyperoxaluria), ethylene glycol	Crystalluria, AKI, and CKD	Crystals are translucent to pale blue fan-like or sunburst shapes within tubules and interstitium with interstitial inflammation and positively birefringent on polarization	Ascorbic acid and orlistat: assure euvolemia during drug therapy, avoid other nephrotoxins; fomepizole and HD for ethylene glycol
Sodium phosphate purgative (oral rather than enema)	AKI and CKD	Granular bluish-purplish crystal deposits with positive von Kossa staining and negative birefringence on polarization	Assure euvolemia before exposure, avoid concomitant NSAIDs, diuretics, and RAS blockers
Triamterene	Crystalluria, AKI, CKD, and nephrolithiasis	Crystals stain yellow/brown on H&E and PAS, silver-positive on JS, and strongly birefringent on polarization	Alkalinize urine, assure euvolemia during drug therapy
Amoxicillin	Crystalluria and AKI	No histologic evidence of intrarenal deposits of amoxicillin crystals on biopsy	Assure euvolemia, adjust drug dose for kidney function
Foscarnet	AKI, hematuria, proteinuria, and CKD	Plates and geometric shapes in dilated capillary loops and tubular lumens associated and positively birefringent on polarization	Assure euvolemia during drug therapy and adjust drug dose for kidney function

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[a]Treatment includes drug discontinuation, intravenous (iv) fluids for hypovolemia, and supportive care including dialysis. H&E, hematoxylin and eosin; HD, hemodialysis; IVF, intravenous fluid; JS, Jones methenamine silver; NSAIDs, nonsteroidal anti-inflammatory drugs; PAS, periodic acid–Schiff; RAS, renin-angiotensin system. Reproduced with permission from Perazella *et al*. 2022.[568]

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4.3. Implementation of kidney protective strategies

Practice Point 4.3.1: Pharmacists should perform medication reconciliation and medication regimen reviews and perform drug and nephrotoxin stewardship for hospitalized children and adults with or at risk of AKI.

Hospitalized children and adults are at risk for medication errors, adverse drug events, and therapeutic failures of inappropriately prescribed medications. Several studies have evaluated the relationship between pharmacist oversight of people in hospital with AKI. Pharmacist interventions in adults have been associated with better processes of care and clinical outcomes, including lower risks of medication errors,[420, 564, 565, 569-571] lower incidence of AKI,[90, 420, 539, 546, 564, 565, 572] and lower AKI severity.[90, 420, 564, 565] One systematic review and meta-analysis of 34 cohort studies or RCTs (n=19,298 participants) evaluating pharmacist interventions for vancomycin management reported a higher rate of attaining drug target concentration, improved SCr monitoring, a lower incidence of vancomycin-induced AKI, and lower mortality associated with pharmacist involvement.[539]

Dedicating pharmacists to medication reconciliation and regular medication regimen reviews can increase healthcare system costs; however, some studies have reported these costs may be offset by lower drug costs resulting from dose modifications.[573] In low-resource hospital settings, where pharmacist services are unavailable, education and training of other available healthcare professionals in drug and nephrotoxin stewardship is an alternative (Table 32).

Medication review and reconciliation have been specifically suggested: i) at ICU/hospital admission and discharge, ii) at time of AKI or AKD identification or change in severity, and iii) when a patient's clinical condition changes.[574] The Work Group agrees with practice points from Section 4.3 Polypharmacy and drug stewardship of the *KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of CKD* and believes the statements below apply to people with AKI and AKD:[17]

i. Perform thorough medication review at transitions of care.
ii. If medications are discontinued during an acute illness, communicate a clear plan of when to restart the discontinued medications to the affected person and healthcare professionals, and ensure documentation in the medical record.
iii. If medications such as metformin, ACEi, ARBs, and SGLT2i are discontinued as a precautionary measure to prevent complications, failure to restart these medications after the event or procedure may lead to unintentional harm.
iv. Educate and inform people with high risk of AKI regarding the expected benefits and possible risks of medications.

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Table 32 | Description of pharmacist interventions and related outcomes for people with or at risk for AKI in various practice settings across the world

Reference	Population	Pharmacist interventions	Outcomes
Hospital setting			
Goldstein SL et al. 2013, 2016, 2020[420, 564, 565]	Pediatrics outside the ICU at a hospital in the U.S. A single center trial, a follow up study and a multicenter study	Facilitate monitoring of SCr with the patient care team for those at risk for AKI (receiving 3 or more nephrotoxins)	• Reduced AKI incidence and severity in multiple studies
Ebah L et al. 2017[572]	32 inpatient wards and 20 specialties in an institution in England	Prompt medication review with discontinuation of potentially nephrotoxic medications as part of a multicomponent team-based intervention	• Drug reviews increased from 48% to 95% in this pre- and post-intervention assessment • AKI incidence reduced
Stoops C et al. 2019[90]	Neonates in the ICU at a hospital in the U.S. (n=476 high exposure events)	Facilitate monitoring of SCr with the patient care team for those at risk for AKI (receiving 3 or more nephrotoxins)	• Reduced nephrotoxin exposure, AKI incidence and severity
Kunming P et al. 2023[539]	Systematic review and meta-analysis of 34 cohort studies and/or randomized controlled trials (n=19,298)	Pharmacist intervention was defined as a pharmacist, or a medical team led by a pharmacist, taking measures to intervene in vancomycin treatment. Pharmacist intervention measures included: (i) recommendation to discontinue vancomycin and/or alternative anti-MRSA agents; (ii) recommendation of initial dose and/or dose adjustment; (iii) therapeutic drug monitoring plan and/or follow-up plan for future monitoring; and (iv) development and implementation of vancomycin dosing nomogram and therapeutic drug monitoring guidelines. Participants in control group did not receive pharmacist intervention or were	• Lower incidence of vancomycin-associated AKI: 7.3% for post- and 9.6% for pre-intervention (OR: 0.52; 95% CI: 0.41–0.67, p <0.00001) • Post-intervention had lower risk of mortality than pre-intervention participants (OR 0.47; 95% CI: 0.31–0.72, p=0.0004).

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		retrospective control prior to pharmacist intervention.	
Polat EC et al. 2022[546]	Adults in an ICU in Turkey (n=150)	While participating in patient care rounds, recommendations included drug selection, drug administration routes, drug dose adjustment, drug-drug interactions, drug-food or interactions, drug side effect management, and drug incompatibility	• AKI incidence reduced
Hou J et al. 2023[575]	Adults with AKI caused by antibiotics in an ICU in China (n=145)	Dose adjustments, drug replacements, and CRRT treatment	• No difference in kidney function outcomes and infection control outcomes between the pre- and post-evaluation

AKI, acute kidney injury; CI, confidence interval; CRRT, continuous renal replacement therapy; ICU, intensive care unit; OR, odds ratio; SCr, serum creatinine; U.S., United States

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Practice Point 4.3.2: Clinical decision support systems (CDSS) can be an effective tool to facilitate drug and nephrotoxin stewardship strategies in children and adults to prevent drug-associated AKI or the development of adverse reactions from drugs excreted by the kidney.

CDSS can aid in identification of people at risk of adverse drug events, optimization of medication management, recognition of drug interactions, and prompt kidney function monitoring through rule-based alerts.[420, 564, 565, 576, 577] CDSS may be useful in preventing medication dosage errors of drugs excreted by the kidney by alerting to overdosed or contraindicated dosages for people in hospital with a decreased GFR.[578-580] Implementation of an alert-based CDSS that focused on concurrent administration of ≥3 nephrotoxins pediatrics in hospital has been shown to result in improved patient outcomes. Further, this CDSS achieved a sustained impact on clinical practice over 3.5 years and remained effective when scaled across multiple pediatric hospitals.[420, 565] CDSS supporting clinical risk stratification enables the early identification of people at risk for development or progression of AKI, allowing for proactive monitoring and intervention. The effectiveness of CDSS may be more effective when alerts are integrated into healthcare professional workflows at the time and place of prescribing decisions, when actionable recommendations are included, and when computer-based.[581, 582]

4.4 Biomarker characterization of drug-related AKI

Practice Point 4.4.1: Biomarkers of tubular damage are approved for monitoring of drug-induced AKI.

Several of the kidney stress and damage biomarkers are detectable within hours after drug-related AKI and may be used to detect AKI before the rise in SCr. The U.S. FDA has qualified a composite of 6 biomarkers for monitoring of drug-induced kidney injury in early-phase clinical trials. This panel, composed of KIM-1, NGAL, clusterin (CLU), cystatin C (cys), N-acetyl-beta-D-glucosaminidase (NAG), and Osteopontin (OPN), is used to detect kidney tubular injury when there is concern about the nephrotoxicity of a drug. This is intended to help in the development of safer and more effective medicines by providing an earlier indicator of kidney response to drug-induced injury than changes in SCr.

Practice Point 4.4.2: Biomarkers may be useful for differentiating mechanisms and etiologies of drug-related kidney diseases in children and adults.

Biomarkers may aid in differentiating among mechanisms and etiologies of AKI among people receiving drugs associated with AKI (Table 33), which may influence management.[241, 583, 584] Serum cystatin C can distinguish non-GFR related increases in SCr (pseudo-AKI) due to the effects of a drug (Table 33) from true AKI because it is unaffected by drug-induced changes in creatinine secretion. An increased SCr but normal cystatin C indicates a drug-induced effect on creatinine generation or tubular secretion (pseudo-AKI), whereas an increase in both SCr and cystatin C is consistent with AKI.[585] Correct differentiation may guide the decision whether to continue or discontinue suspected drugs.

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Urine CXCL9 may offer a reliable, noninvasive biomarker for identification of AIN.[241] High urine CXCL9 levels strongly correlate with biopsy proven AIN. Urinary CXCL9:creatinine values <14.2 ng/g could be used to rule out AIN with negative predictive values exceeding 94% while values >58.9 ng/g could be used to rule in AIN. However further validation and approval for clinical use is needed.

Table 33 | Potential use of biomarkers to distinguish etiology of drug-related acute kidney diseases

Biomarker	Use	Comment
Plasma cystatin C	Differentiate non-GFR related increases in serum creatinine (pseudo-AKI) due to a drug from actual AKI	A normal cystatin C when SCr is increased is consistent with non-GFR related effects of a drug due to i) effects on tubular creatinine secretion (e.g., trimethoprim), ii) effects on analytic measurement of creatinine, or iii) effects on creatinine generation.
Urine chemokine C-X-C motif ligand 9 (CXCL9)	Identifying AIN. Differentiate drug related AIN from other etiologies	CXCL9: creatinine value<14.2 ng/g could be used to rule out AIN, while >58.9 ng/g could be used to rule in AIN

AIN, acute interstitial nephritis; AKI, acute kidney injury; NSAID, nonsteroidal anti-inflammatory drugs; SCr, serum creatinine

4.5. Management of drugs eliminated by the kidneys

Practice Point 4.5.1: Dosing of drugs excreted by the kidneys should not be based on creatinine clearance or glomerular filtration rate (GFR) estimated using equations that assume a steady state of creatinine production and clearance in children and adults children with developing or resolving AKI or AKD.

Practice Point 4.5.2: Trends in SCr and urine output should be used to guide dosing of drugs excreted by the kidney. In adults with AKI, calculation of a KeGFR may be useful when sufficient SCr measurements are available.

Ideal methods for measuring GFR use urinary clearance of exogenous compounds such as inulin or iohexol but these approaches are not practical to guide drug dosing in routine clinical practice due to costs and technical challenges. Measurement of urinary creatinine clearance with timed urine collections is an option to estimate GFR but is limited by overestimation of true GFR by 10%–20% due to tubular secretion of creatinine and inaccuracies in timing of collections.

The Work Group agrees with the following practice point related to drug dosing from the *KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of CKD* and believes it also applies to people with AKI and AKD.

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Practice Point 4.5.3: Consider and adapt drug dosing in people where GFR, non-GFR determinants of the filtration markers, or volume of distribution are not in a steady state.

In the context of AKI, it is important to recognize that GFR estimating equations such as the Cockcroft-Gault, MDRD, and CKD-EPI equations were developed and validated for people with CKD and assume a steady state of SCr.[586, 587] They will overestimate a person's GFR when SCr is rising (potentially resulting in drug overdosing) and underestimate GFR when SCr is falling (potentially resulting in drug underdosing). For people with AKI, it is important to consider trends in SCr and urine output when dosing drugs excreted by the kidney. Initial dosing may start with a standard dose based on a person's eGFR before the AKI episode, or a dose that would be appropriate for severely abnormal kidney function, depending on the clinical situation. A person who is anuric should be considered to have a GFR <10 ml/min.[588] Changes in SCr and urine output along with therapeutic drug monitoring if available, can be used to guide and adjust subsequent doses.

KeGFR accounts for the rate of change in SCr over time, providing a more accurate real-time estimate of GFR that can be used to guide drug doses with changing SCr values accompanying AKI.[589] In 1 study, use of a KeGFR equation resulted in changes in drug dosing in approximately 20% of participants compared to non-kinetic eGFR equations.[590] At this time, no one equation can be endorsed over another and all have limitations.[574, 587]

Practice Point 4.5.4: Assess and adjust drug dosing in children and adults receiving CRRT based on drug-, patient-, and RRT-related factors (Table 34).

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Table 34 | Drug-, patient-, and RRT-related factors to consider when determining drug doses for people receiving CRRT

Drug-related factors	• Medications eliminated by the kidney with volume of distribution <0.7 l/kg and/or protein-binding <80% are likely to be removed with CRRT and may require supplemental dosing with CRRT use. • Molecular weight of a drug is an important consideration when using CRRT diffusive techniques compared to convective techniques because the diffusion coefficient, or saturation coefficient (Sd or SA) is inversely proportional to the molecular weight such that, as the SA decreases, the molecular weight increases. Conversely, convective transport across modern membranes is independent of molecular weight in convective hemofiltration techniques.[591, 592] • Most drugs have a molecular weight <2000 Daltons and are removed to some extent with newer high-flux and super high-flux dialyzers that have a pore size between 10,000–30,000 (likely diffusion technique, as well) • Administering supplement doses for drugs with >30%–40% post-hemodialysis removal is suggested. • Optimal dosage regimens for medications eliminated by the kidney and nephrotoxic medications (e.g., digoxin, vancomycin, aminoglycosides, and calcineurin inhibitors) can be achieved by performing therapeutic drug monitoring in people who are critically ill receiving RRT. • For antibiotic dose adjustments during AKI and RRT, be mindful of pharmacokinetic target concentration attainment and optimizing pharmacodynamic effects with consideration to the antibiotic concentration and time dependent bactericidal effects.
Patient-related factors	• Hypoalbuminemia affects drugs that are highly bound to albumin, by increasing free fraction of the drug leading to increased clearance and volume of distribution. • Fluid resuscitation, and capillary leak increase the volume of distribution of hydrophilic drugs, for example in people with sepsis. This may require a loading dose in the range of 25% more than usual. • People with significant urine output (e.g., >20 ml/hr or 500 ml/day), should have clearance from the residual urine volume added to RRT clearance calculations to determine total drug clearance for the person. • Non-kidney drug clearance can be affected by RRT for AKI. Drugs eliminated by the liver and formed metabolites may accumulate during AKI, while RRT can possibly increase CYP3A4 activity. Estimating non-kidney clearance in people who are critically ill is challenging without assessing serum drug levels due to the various pathways involved in drug metabolism and clearance.

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*RRT-related factors**	• Effluent flow rate determines drug clearance in CRRT given it is slower than the blood flow rate and more drug removal occurs with faster effluent flow rates.[593] • If RRT is <25% of the patient's clearance (sum of residual kidney and non-kidney), then RRT appears not to add significantly to person's drug elimination process.[592] • RRT modality affects drug clearance such that when a similar blood flow rate is used, drug elimination by RRT can be ordered from the highest to lowest as follows: CVVHDF > CVVH > IHD.[591] • For CRRT, clearance can be estimated by checking the run time and subtracting the down time. • Replacement fluid is commonly provided in convective techniques of RRT, either pre- or post-dilution modes. Pre-dilution mode reduces drug clearance more than post-dilution by approximately 15%.[591] • Hemofilter lifespan can affect solute clearance (i.e., older filters provide less clearance). • Membrane types affect adsorption and adsorption is inversely correlated to effluent flow rate.[591, 594, 595] • Drug removal estimates for IHD are not equivalent to CRRT. When suing drug removal estimates from primary or secondary sources, it is important to confirm that the RRT modality, technique, and settings are the same as the patient scenario being evaluated.

*RRT related factors do not apply to children due to the size of the extracorporeal volume. AKI, acute kidney injury; CRRT, continuous renal replacement therapy; CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration, IHD, intermittent hemodialysis, PIRRT, prolonged intermittent renal replacement therapy; RRT, renal replacement therapy

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4.6. AKI following other nephrotoxic exposures

Practice Point 4.6.1: In children and adults presenting with community-acquired AKI, perform a thorough social, occupational, and demographic history to understand potential exposures to pesticides and environmental exposures as a possible cause of AKI.

Each year, millions of pounds of pesticides are used in agriculture to manage a variety of threats to crops. These chemicals present potential occupational exposure risks that healthcare professionals should be aware of, particularly in relation to environmental toxicity to the kidney. It is known that occupational exposure, even for short durations, can increase the incidence of AKI.[596, 597] Also, residential exposure for people living close to agricultural lands can be a concern for adverse effects.[598, 599] The incidence of AKI is increasing in younger adults in low-to-middle resource settings due to accidental and intentional organophosphate poisoning.[600] Awareness by healthcare professionals can promote detection of pesticide-associated AKI, and educate people about occupational risks and reduce exposures.

Practice Point 4.6.2: Determine and limit the use of natural products that have the potential to contribute to AKI and AKD through patient-centered discussions.

Over 80% of the population in low- and middle-resource settings use herbal and traditional medicines because of cultural beliefs, economic considerations, and accessibility.[601] Regulations surrounding the approval of natural products for public consumption are less stringent than prescription medications, and adverse events often go unreported. The true incidence of AKI attributable to natural products is unknown. There have been several case reports and reviews suggesting a causation between several natural products presented in Table 35.

Table 35 | Examples of nephrotoxicity associated with natural products[602]

Scientific (Latin) name	Common (English) name	Kidney manifestations/mechanism
Aristolochia species	Aristolochic	Interstitial nephritis/fibrosis, Tubular atrophy/defect, Fanconi syndrome, urothelial malignancies
Artemisia absinthium	Wormwood oil	AKI secondary to seizure-induced rhabdomyolysis, acute tubular injury
Atractylis gummifera	Glue thistle	Acute tubular injury
Averrhoa carambola	Starfruit	Acute tubular injury, oxalate nephropathy, nephrolithiasis, obstructive nephropathy
Cassia angustifolia	Senna fruit	Proximal and distal renal tubular acidosis, diabetes insipidus
Cleistanthus collinus	Oduvan	Type 1 renal tubular acidosis with severe hypokalemia
Crataegus orientalis	Hawthorne	AIN, AKI
Dioscorea quinqueloba or quartiniana	Yam	Biopsy-proven AIN, acute tubular injury

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Scientific (Latin) name	Common (English) name	Kidney manifestations/mechanism
Ephedra species	Ma-huang	Stones of ephedrine and ephedrine metabolites, AKI secondary to rhabdomyolysis
Euphorbia paralias	Euphorbia	AKI
Glycyrrhiza glabra	Licorice	AKI secondary to hypokalemia-induced rhabdomyolysis, Fanconi's tubulopathy
Hedeoma pulegioides	Pennyroyal	Acute tubular injury, Hepatorenal syndrome
Larrea tridentata	Chappara	Kidney cysts, renal cell carcinoma
Thevetia peruviana	Yellow oleander	Acute tubular injury, hepatorenal syndrome
Tribulus terrestris	Puncturevine	Acute tubular injury, AIN not excluded
Uncaria tomentosa	Cat's claw	Acute interstitial nephritis
Vaccinium macrocarpon	Cranberry	Nephrolithiasis

Abbreviations: AKI, acute kidney injury; AIN, acute interstitial nephritis

4.7. Contrast-associated AKI (CA-AKI): Recognition

Practice Point 4.7.1: Consider the differential diagnosis of post-contrast AKI, which may have causes other than contrast exposure.

Contrast-associated AKI (CA-AKI) refers to AKI following parenteral administration of iodinated radiocontrast media. The reported incidence of CA-AKI has varied in the literature with use of different definitions, with some reviews reporting it as the third most common cause of AKI in hospitalized adults. The attribution of contrast exposure to AKI continues to be a source of debate; however, CA-AKI has been consistently associated with adverse short- and long-term outcomes.

The Work Group agrees with the suggestion from Section 4.4 of the *KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of CKD* that the term "contrast-associated AKI" be used to recognize the broader differential diagnosis for the etiology of AKI in many such cases, which may or may not be solely attributable to contrast.[17] The presumption that all AKI following contrast administration is CA-AKI has led to a lack of specificity in case definitions and associated epidemiology; indeed, some have questioned the existence and clinical importance of CA-AKI.[603] Nonetheless, in 2023, the American College of Radiology (ACR) Contrast Manual stated the position of the ACR Committee on Drugs and Contrast Media that CA-AKI is a real, albeit rare, entity.[604] The Work Group concurred with this statement while recognizing that CA-AKI includes other etiologies of AKI following radiocontrast exposure, including multifactorial causes (combined with radiocontrast).

4.8. Contrast-associated AKI: Risk assessment

Practice Point 4.8.1: Use validated tools to assess the risk of AKI in adults receiving intra-arterial radiocontrast for cardiac procedures.

The Work Group endorses Practice Point 4.4.1 from the *KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of CKD* to assess the risk of CA-AKI with intra-arterial contrast for cardiac procedures using validated tools.[17] Many models

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include patient-related risk factors for CA-AKI in addition to eGFR, and these models have been validated for estimating risk in people with or without CKD.

The reported risk of CA-AKI is higher with procedures involving intra-arterial administration compared with intravenous administration of radiocontrast. This difference in risk may be due to diversities in patient populations or to variations in the nephrotoxicity of intra-arterial delivery of contrast material. Commonly reported patient-related risk factors for CA-AKI are age, baseline kidney function, medical history (diabetes, cardiovascular diseases, and heart failure), presenting with acute coronary syndrome, and cardiac function (New York Heart Association Class, left ventricular ejection fraction, and Killip class).[605] Risk also varies with procedural factors, with highest risk associated with interventional (rather than diagnostic) coronary angiography (i.e., percutaneous coronary interventions with balloon angioplasty ± coronary stent placement) for acute myocardial infarction (MI). In addition to intra-arterial dye administration and arterial instrumentation, this may relate to the higher volume of contrast used in interventional procedures and hemodynamic instability associated with the clinical situation. Other procedure-related risk factors include the osmolarity and volume of dye used (including repeated studies).

There are several comprehensive systematic reviews of validated risk scores that can be used to predict the risk of CA-AKI following coronary angiography (Table 36).[605-607] Validated models are available to predict AKI defined by KDIGO SCr criteria, as well as to predict RRT.[606] Newer models have generally demonstrated better calibration in more recent validation studies.[607] Most recently, Feng and colleagues conducted a systematic review of the published scores to predict CA-AKI after coronary angiography;[605] their analysis of 45 studies found a pooled C-statistic of 0.83 (95% CI: 0.82–0.84), with pooled sensitivity of 0.74 (95% CI: 0.70–0.78) and pooled specificity of 0.78 (95% CI: 0.75–0.82), with substantial heterogeneity in discrimination between prediction model studies. Notably, there has been no meaningful improvement in estimates of model discrimination despite publication of new models. The variables that have been repeatedly included in different prediction models are listed in Table 36.

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Table 36 | Predictive variables in included prediction models

Grouping variables	Total occurrence, No. (%)[a]	Predictive variables
Baseline kidney function	56 (14.1)	CKD, eGFR, CCR, serum creatinine, cystatin C, and serum BUN
Past medical history	50 (12.6)	Prior cardiac shock, prior cardiac arrest, prior MI, prior CVD, prior heart
Age	37 (9.3)	Age
CAD presentation	33 (8.3)	AMI, PCI status, ACS subtype, PCI indication, CAD presentation, multivessel PCI, emergency procedure, operation, and time to reperfusion
Cardiac function	22 (5.5)	NYHA class, LVEF, and Killip class
Blood pressure	20 (5.0)	SBP, hypotension, hypertension, and shock
Anemia	17 (4.3)	Anemia
CBC indices	15 (3.8)	SII, WBC count, neutrophil percentage, platelet count, RDW, NLR, lymphocyte count, and P-LCR
Contrast medium volume	15 (3.8)	Contrast medium volume
Cardiac biomarker	14 (3.5)	CK-MB, troponin I, myoglobin, and NT-pro-BNP
Liver function indices	12 (3.0)	Serum albumin, serum total bilirubin, LDH, and total protein
IABP	12 (3.0)	IABP
Inflammation biomarkers	12 (3.0)	Procalcitonin, Interleukin-18, and hsCRP
Blood lipid indices	11 (2.8)	Triglyceride, LDL-C, HDL-C, total cholesterol, and triglyceride-glucose index
Sex	8 (2.0)	Sex
Weight	7 (1.8)	Weight
Drug use	7 (1.8)	Loop diuretics use, β-blocker, antimicrobial drugs, and metformin use
Blood glucose	6 (1.5)	Blood glucose and HbA1C
Heart rate	5 (1.3)	Heart rate
Other	38 (9.6)	Height, uric acid, big ET-1, soluble klotho, KIM-1, osteopontin, CD5 antigen-like, free triiodothyronine, CHA2DS2-VASc score, AGEF score, Mehran score, serum sodium, serum calcium, serum potassium, fibrinogen-to-albumin ratio, fibrinogen, AT-III, INR, maximum AAA diameter, urinary system contrast blush grade, kidney PI, proteinuria, years since drinking, and admission source

AAA, abdominal aortic artery; ACS, acute coronary syndrome; AGEF, age, estimated glomerular filtration rate and ejection fraction; AMI, acute myocardial infarction; AT-III, antithrombin III; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CAD, coronary artery disease; CBC, complete blood count; CCR, creatinine clearance rate; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes, prior stroke/transient ischemic attack–vascular disease, age 65–74 years, sex category; CKD, chronic kidney disease; CK-MB, creatine kinase-MB; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ET-1, endothelin-1; HbA1c, hemoglobin A_{1c}; HDL-C, high-density lipoprotein cholesterol; hsCRP, highly sensitive C reaction protein; IABP, intra-aortic balloon pump; INR, international normalized ratio; KIM-1, Kidney injury molecule-1; LDH,

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lactate dehydrogenase; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NLR, neutrophil-to-lymphocyte ratio; NT-pro-BNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PI, peaking intensity; P-LCR, platelet large cell ratio; PVD, peripheral vascular disease; RDW, red blood cell distribution width; SBP, systolic blood pressure; SII, systemic immune-inflammatory index; WBC, white blood cell. [a]Numbers in parentheses represent percentages of each combined variable in the total occurrence of predictive variables. Reproduced from Feng et al. 2025.[605]

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Practice Point 4.8.2: Assess children and adults being considered for intravenous radiocontrast administration for risk factors for contrast-associated AKI, and in particular screen for preexisting impairment of kidney function.

The KDIGO 2012 Clinical Practice Guideline for AKI suggested assessment of the risk of CA-AKI, and specifically screening for "pre-existing impairment of kidney function" in all people for whom a procedure requiring intravascular (intra-arterial or intravenous) radiocontrast is being considered.[608] The Work Group continues to support the assessment of risk for CA-AKI in all people being considered for intravascular contrast. However, intravenous contrast administration for computed tomography (CT) scans generally has lower risks for CA-AKI than intra-arterial administration for coronary angiography for several reasons. Cardiac angiography differs from intravenous contrast medium administration in 4 major ways: 1) the injection is intra-arterial and suprarenal instead of through a peripheral vein, 2) the injection requires a catheter which can dislodge atheroemboli, 3) the contrast medium dose to the kidneys will be more abruptly delivered and concentrated resulting in greater "first-pass" exposure, and 4) people undergoing coronary angiography may have other chronic comorbidities and acute insults (e.g., acute ventricular dysfunction during MI) that predispose to the development of CA-AKI. Accordingly, risk estimates from models developed to predict the risk of CA-AKI following coronary procedures can be inaccurate for people receiving intravenous radiocontrast.

Multiple current published guidelines for risk assessment for CA-AKI following intravenous radiocontrast administration in adults identify kidney function (i.e., reduced eGFR in CKD or presence of AKI), along with some other clinical variables as important risk factors. The 2020 joint Consensus statement from the ACR and National Kidney Foundation (NKF) defined risk factors for CA-AKI following intravenous contrast as eGFR<30 ml/min per 1.73 m^2 or AKI, or eGFR 30–44 ml/min per 1.73 m^2 with multiple risk factors;[609] this criteria was also included part of the *KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of CKD*.[17]

The *KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of CKD* listed commonly accepted risk factors for CA-AKI in 2 broad categories,[17, 610] including abnormal kidney function (CKD or AKI), but also a variety of other patient-related and procedure-related risk factors (Table 37). Among published reports of risk factors for CA-AKI in adults following CT scans, CKD was the major risk factor, particularly CKD with cancer (CKD G4–G5: OR: 3.76; CKD G3b: OR 1.93) and CKD G3b–G4 without cancer (OR: 1.42–1.9; CKD G5: 1.45; NS). Other significant risk factors included shock (OR: 2.15), and congestive heart failure (CHF) or proteinuria with cancer (OR: 1.7).[611, 612]

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Table 37 | Risk factors for CA-AKI in adults

Patient-associated risk factors	Procedure-associated risk factors
Reduced GFR, acute or chronic in adults[a]	High-osmolar contrast
Diabetes mellitus[b]	Large volume of contrast
Reduced intravascular volume	Serial contrast procedure
Concomitant nephrotoxic medications	Intra-arterial procedures

[a]Defined as estimated glomerular filtration rate <45 ml/min per 1.73 m^2 with other risk factors or eGFR <30 ml/min per 1.73 m^2. [b]Augments risk in people with underlying kidney function impairment. CA-AKI, contrast-associated acute kidney injury; GFR, glomerular filtration rate. Reproduced from Cashion W, Weisbord SD 2022.[610]

4.9. Contrast-associated AKI: Prevention

4.9.1. Choice of imaging technique

Practice Point 4.9.1.1: Following a risk assessment, the decision to administer intravascular contrast for a diagnostic or interventional procedure should be made weighing the risks versus benefits of the procedure. Where the perceived benefit exceeds the risk, contrast procedures should not be deferred or delayed. However, when possible, alternative imaging methods should be used for people with or at high risk of contrast-associated AKI (CA-AKI) (Figure 12).

An assessment of risks versus benefits is important with all diagnostic and interventional procedures involving radiocontrast administration. It is desirable to avoid iodinated contrast media in people with or at high risk of AKI if adequate diagnostic tests or therapeutic interventions can be obtained without contrast administration. However, procedures involving the administration of contrast may be necessary for the management of many clinical syndromes. When selecting imaging methods, it is important to evaluate the potential impact of limiting or postponing access to diagnostic and therapeutic contrast imaging procedures.

This practice point aligns with Practice Point 4.4.1 from the *KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of CKD*, approaching the decision for contrast administration on an individualized basis, in which the risk of CA-AKI following administration of radiocontrast should be balanced against the risk of inadequate imaging and therapy following alternative imaging tests.[17]

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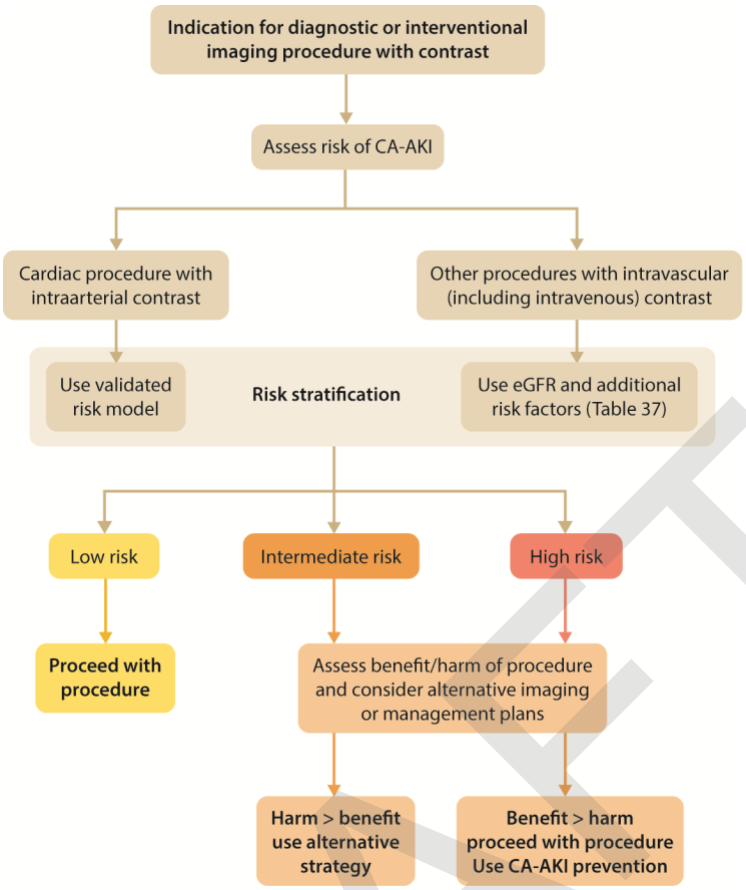
Indication for diagnostic or interventional imaging procedure with contrast
Assess risk of CA-AKI
Cardiac procedure with intraarterial contrast
Other procedures with intravascular (including intravenous) contrast
Use validated risk model
Risk stratification
Use eGFR and additional risk factors (Table 37)
Low risk
Intermediate risk
High risk
Proceed with procedure
Assess benefit/harm of procedure and consider alternative imaging or management plans
Harm > benefit use alternative strategy
Benefit > harm proceed with procedure Use CA-AKI prevention

Figure 12 | Approach to risk assessment for CA-AKI with diagnostic or interventional contrast imaging procedures. CA-AKI, contrast-associated acute kidney injury

Practice Point 4.9.1.2: Iso-osmolar or low-osmolar iodinated contrast media may be used in children and adults at risk of CA-AKI (*1B*).

High-osmolar contrast agents are no longer used for intravascular imaging in clinical radiology and have been replaced globally by safer, more tolerable low-osmolar and iso-osmolar alternatives with a lower risk of AKI. Whether iso-osmolar agents (~290 mOsm/kg) have a lower risk of AKI than low-osmolar agents (322–900 mOsm/kg) remains uncertain. A meta-analysis of 25 RCTs comparing the risk of AKI between iso- and low-osmolar agents reported a pooled RR of 0.80 (95% CI: 0.61–1.04). Subgroup analyses of trials restricted to people with abnormal kidney function receiving intra-arterial contrast administration suggested potential for differences between specific low-osmolar versus iso-osmolar agents. The risk of AKI was greater for the low-osmolar agent iohexol than for the iso-osmolar agent iodixanol (RR: 0.38; 95% CI: 0.21–0.68), while there was no difference between iodixanol and other (non-iohexol) low-osmolar agents (RR: 0.95; 95% CI: 0.50–1.78). A subsequent meta-analysis of 10 RCTs restricted to people with CKD reported no difference in AKI with iso-osmolar compared to low-osmolar agents (RR: 0.72; 95% CI: 0.50–1.04). The effect estimate was attenuated when the analysis was restricted to large RCTs with more than 250 participants, used as a surrogate of trial quality (RR: 0.93; 95% CI: 0.66–1.30).

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The existing evidence base therefore has not established a benefit to use of iso-osmolar over low-osmolar agents. Accordingly, the choice between low-osmolar or iso-osmolar contrast agents may depend on availability and cost, particularly in lower- and lower-to-middle- resource settings. It is appropriate to use the least nephrotoxic agent available for people at increased risk of CA-AKI. This practice is consistent with statements published by the ACR,[604] Canadian Association of Radiology,[613] and European Society of Urogenital Radiology.[614]

Practice Point 4.9.1.3: For children and adults at high risk of CA-AKI, use the lowest possible dose of intravascular radiocontrast to achieve adequate imaging.

Contrast dose is associated with risk of CA-AKI; however, this relationship is complex and modified by patient and procedural factors. While risk generally increases with dose, small increases in contrast volume may lead to disproportionate increases in AKI risk in high-risk people, while even moderate-to-high contrast volumes may not cause AKI in low-risk people (Figure 13). Furthermore, recent studies illustrate that the relationship between contrast dose and CA-AKI is non-linear across the range of contrast volumes and heterogeneous according to a patient's preprocedural risk. A variety of procedural strategies can minimize contrast administration, including imaging and guidance technologies (e.g., intravascular ultrasound on optical coherence tomography), fluoroscopy optimization, injection techniques, and catheter selection. Automated contrast injectors can lower contrast volumes but the effect depends heavily on how they are used with a need for training and optimization of settings.[615] Procedural planning and staging of procedures (limiting the extent of contrast used in a single session) can further help to limit the dose of contrast exposure.

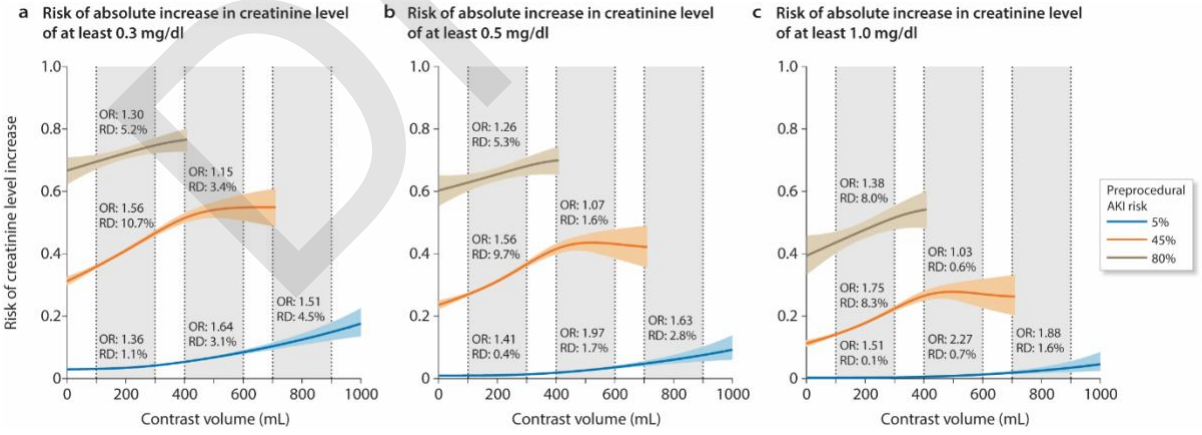
a Risk of absolute increase in creatinine level of at least 0.3 mg/dl
b Risk of absolute increase in creatinine level of at least 0.5 mg/dl
c Risk of absolute increase in creatinine level of at least 1.0 mg/dl
Risk of creatinine level increase
Contrast volume (mL)
OR: 1.30 RD: 5.2%
OR: 1.15 RD: 3.4%
OR: 1.56 RD: 10.7%
OR: 1.51 RD: 4.5%
OR: 1.36 RD: 1.1%
OR: 1.64 RD: 3.1%
OR: 1.26 RD: 5.3%
OR: 1.07 RD: 1.6%
OR: 1.56 RD: 9.7%
OR: 1.41 RD: 0.4%
OR: 1.97 RD: 1.7%
OR: 1.63 RD: 2.8%
OR: 1.38 RD: 8.0%
OR: 1.03 RD: 0.6%
OR: 1.75 RD: 8.3%
OR: 1.51 RD: 0.1%
OR: 2.27 RD: 0.7%
OR: 1.88 RD: 1.6%
Preprocedural AKI risk
5%
45%
80%

Figure 13 | Prediction of risks of AKI as a function of contrast volume and preprocedural AKI risk in percutaneous coronary intervention. Risks of absolute increase in creatinine were calculated for patients with preprocedural AKI risks of 5%, 45%, and 80%. Odds ratios (ORs) and absolute risk differences (RDs) of AKI risks are given for increases in contrast volume from 100 to 300 ml, from 400 to 600 ml, and from 700 to 900

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ml. The colored bands indicate 95% CIs. To convert creatinine to micromoles per liter, multiply by 88.4.[616] AKI, acute kidney injury

Several calculations and multivariable modeling approaches have been developed to estimate the risk of CA-AKI.[617, 618] Estimation of a safe contrast limit is a strategy to prevent excessive exposure to contrast media. These limits are often calculated based on patient-specific parameters, such as preprocedural kidney function in addition to other patient risk factors, and are intended to give individualized, actional estimates of safe contrast volume dose for planning procedures (Table 38). The Contrast Reducing Injury Sustained by Kidneys (RISK) trial, a large, multicenter, stepped-wedge, cluster RCT in people undergoing coronary angiography and intervention, demonstrated that a multimodality approach providing CDSS accompanied by audit and feedback on contrast volume significantly reduced the incidence of CA-AKI.[153] Secondary outcomes included a significant reduction in the contrast dose administration, suggesting this may have mediated the reduction in AKI incidence observed. Subsequent trials confirmed that multimodality interventions that incorporate strategies to reduce contrast dye dosing along with intravenous hydration strategies can be implemented in health systems successfully and achieve a lower incidence of CA-AKI.[619]

Table 38 | Examples of strategies to estimate contrast volume doses with lower risk of CA-AKI

Strategy	Calculation	Targets and CA-AKI risk
Calculation MACD	MACD = 3 × eGFR in ml/min per 1.73 m²	MACD 1.0–1.5: OR 1.60; 95% CI: 1.29–1.97, MACD 1.5–2.0: OR: 2.02; 95%CI 1.45–2.81 MACD >2.0: OR: 2.94; 95% CI 1.93–4-48[620]
Monitoring of CV/CrCl intraprocedurally	CV/CrCl	CV/CrCl of >3.7: OR: 3.84; 95% CI: 2.0–7.3)[621]
Decision support tools using multivariable equations to estimate individualized safe contrast limits	Multivariable predictive models can be used to obtain estimates of CA-AKI according to contrast volume and preprocedural risk. Safe contrast limits can be calculated from the contrast term in the model and use to target specific (e.g., 10%) relative risk reductions	Predictive models for the association of contrast volume with the risk of AKI demonstrate a non-linear association along the spectrum of contrast volume and variation according to patient preprocedural AKI risk.[616, 618, 622] These models have been implemented in EHRs to give personalized decision support to guide contrast dosing during interventional procedures.[153]

AKI, acute kidney injury; CA-AKI, contrast-associated acute kidney injury; CV, contrast volume; CrCl, creatinine clearance; EHR, electronic health record; MACD, maximum allowable contrast dose

4.9.2. Contrast-associated AKI Prevention: Fluid administration

Practice Point 4.9.2.1: For children and adults at high risk of CA-AKI, incorporate volume status assessment into intravenous hydration management strategies to reduce the risk of AKI.

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Volume depletion is a risk factor for CA-AKI. Accordingly, the prophylactic administration of intravenous crystalloids to avoid hypovolemia in people at high risk of CA-AKI has been a standard practice for decades. However, the clinical significance of small acute changes in SCr that define CA-AKI has been questioned in recent years. This has led to reassessment of the benefits versus harms of empiric prophylactic volume expansion to prevent CA-AKI, even in higher risk groups. Furthermore, the growing literature demonstrating that volume overload and congestion can cause or worsen AKI (in addition to potentially causing acute pulmonary edema) has also raised awareness of the potential importance of personalized fluid management in this setting. Recent evidence suggests that strategies that provide more precise assessment of volume status may reduce the incidence of CA-AKI by individualizing fluid management.

In standard clinical practice, the assessment of volume status uses medical history, physical examination, and clinically available tests (including B-type natriuretic peptide, chest x-ray) to determine if volume overload is present, in which case prophylactic hydration may be contraindicated. Multiple trials concerning the approach to volume assessment and fluid management to reduce the risk of CA-AKI have been conducted recently. Findings suggest the use of hemodynamic monitoring or volume assessment to guide fluid administration for CA-AKI prophylaxis may reduce CA-AKI incidence, including with both invasive monitoring[623, 624] and noninvasive assessment methods.[625, 626]

A systematic review and network meta-analysis examined the effects of different hydration strategies for the prevention of CA-AKI. From analysis of 60 eligible RCTs, hemodynamic-guided hydration (OR: 0.41; 95% CI: 0.18–0.93), and device-guided matched hydration with forced diuresis guided by urine flow rate (UFR) (OR: 0.32; 95% CI: 0.14–0.7) significantly reduced the incidence of CA-AKI.[625] A subsequent meta-analysis by Cossette *et al*. included 13 RCTs of participants undergoing coronary angiography or percutaneous coronary intervention (PCI) evaluating tailored intravenous hydration strategies using either hemodynamic monitoring or UFR replacement to guide crystalloid administration. There were significant reductions in incidence of CA-AKI (RR: 0.56; 95% CI: 0.46–0.69, P<0.00001), and of major adverse cardiac events (MACE) (RR: 0.57; 95% CI: 0.42–0.78, P=0.0005) with tailored compared to non-tailored intravenous hydration.[627] This recent evidence suggests that the efficacy and safety of intravenous crystalloid administration for CA-AKI may be improved when guided by these tailored approaches.

Hemodynamic-guided hydration may be achieved using invasive approaches, including left ventricular end diastolic pressure (LVEDP) measurement during cardiac catheterization[623] or continuous central venous pressure monitoring[624] or noninvasive approaches, including bioimpedance (Table 39).[626] Reports of the effects of matched hydration to urine output with forced diuresis are from studies completed using a specific medical device. This strategy may be challenging to implement without such a device. Prophylactic diuretic administration is not recommended to prevent CA-AKI, and caution is

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warranted if attempting to implement these strategies without an established protocol or device.

Table 39 | Hydration strategies to prevent CA-AKI

Hydration strategy	Measurement	Intravenous fluid administration protocol
Hemodynamic guided	Left ventricular end diastolic pressure (LVEDP)	0.9% sodium chloride i.v. bolus infusion at 3 ml/kg for 1 h before the procedure, then rate adjusted according to LVEDP: 5 ml/kg/h for LVEDP <13 mm Hg, 3 ml/kg/h for LVEDP 13–18 mm Hg, and 1.5 ml/kg/h for LVEDP >18 mm Hg for 4 h after procedure[623]
	Central venous pressure (CVP)	0.9% sodium chloride i.v. adjusted hourly according to CVP: 3 ml/kg/h for CVP <6 cm H_2O, 1.5 ml/kg/h for CVP 6–12 cm H_2O), and 1 ml/kg/h for CVP >12 cm H_2O for 6 hours pre-procedure and 12 hours post-procedure[624]
	Bioimpedence vector analysis (BIVA)	0.9% sodium chloride at 2 ml/kg/h for 12 h before and after the procedure for people with a low BIVA level (<315 Ohm/m for males, <380 Ohm/m for females) for 12 h before and after the procedure) or double volume saline (2 ml/kg/h). The infusion rate was halved for people with an ejection fraction <40%.[626]
Device guided	Matched hydration with forced diuresis using urine output from Foley catheter	0.9% sodium chloride i.v. bolus of 250 ml over 30 min followed by an i.v. furosemide bolus of 0.5 mg/kg preprocedure. Injection of contrast media deferred until urine flow rate >300 ml/h. Matched hydration to urine output throughout procedure and up to 4 h after the procedure. Matched hydration during and up to 4 hours post-procedure achieved by initial i.v. infusion 200 ml/h, followed by adjustment of infusion rate to match the urine output after every 5 min.[628]

CA-AKI, contrast-associated acute kidney injury; i.v. intravenous

Recommendation 4.9.2.1: For adults at high risk of AKI without fluid overload undergoing intravascular iodinated contrast-based procedures, we recommend prophylactic periprocedural volume expansion with 0.9% saline over hypotonic solutions (e.g., 0.45% saline), sodium bicarbonate, or no intravenous hydration *(1B)*.

This recommendation places a high value on reducing the risk of CA-AKI, specifically when patient- or procedure-associated risk factors or risk prediction models identify people as being at high risk of CA-AKI. This recommendation is supported by systematic reviews that demonstrate a lower incidence of CA-AKI among adults who received intravenous *isotonic crystalloids compared to no hydration, particularly among high-risk adults receiving coronary procedures. Sodium bicarbonate did not reduce the incidence of CA-AKI compared to 0.9% saline in high quality trials. The large landmark Prevention of Serious Adverse Events Following Angiography (PRESERVE) trial was conducted in adults undergoing coronary angiography with intra-arterial contrast and showed no difference in a composite of death, dialysis, or persistent abnormal kidney function at 90 days between the 0.9% saline versus bicarbonate treated cohort.[629] Similarly, there was no difference in the largest trial in*

critically ill participants receiving intravenous contrast for CT scanning or arteriography.[630] *This recommendation places a lower emphasis on the additional resource use and costs of providing intravenous hydration before and after contrast-imaging procedures.*

Key information

Balance of benefits and harms

For this guideline, we performed an updated systematic review and meta-analyses of RCTs that compared various forms of hydration, including no hydration for CA-AKI prevention. These were built on a systematic review of hydration versus no hydration and a network meta-analysis of different fluids.[625, 631] The majority of studies were conducted in participants undergoing coronary angiography. There is less evidence regarding the risk of AKI in people undergoing intravascular contrast imaging. The certainty of evidence was downgraded due to some methodological issues with the trials and a very imprecise effect estimate.

We identified 7 RCTs that compared intravenous crystalloids versus no hydration, which included 3258 participants, that found consistent evidence of a reduction in CA-AKI incidence with intravenous crystalloid hydration (RR: 0.64; 95% CI: 0.54–0.76) (Supplementary Table S71).[625, 631, 632] Across 6 of the RCTs with 2475 participants, mortality was also lower with intravenous hydration (RR: 0.57; 95% CI: 0.33–0.98), but the estimate for risk of RRT was imprecise (across 3 RCTs with RRT events). Included in the meta-analyses, the A MAastricht Contrast-Induced Nephropathy Guideline (AMACING) trial was a noninferiority RCT that compared pre- and post- procedure hydration with intravenous 0.9% saline versus no hydration in 660 adults with an eGFR between 30–59 ml/min per 1.73 m^2 receiving elective intra-arterial (48%) or intravenous (52%) contrast.[633] The AMACING trial concluded noninferiority of no hydration compared to intravenous hydration in preventing CA-AKI and found that hydration increased costs in this population. However, this noninferiority trial recruited fewer participants than originally planned and had a lower incidence of CA-AKI (2.6%) than projected. Trials incorporated in our systematic review and others included higher risk participants undergoing coronary intervention with an average incidence of CA-AKI of 14% across all studies. Given the heterogenous findings between the lower risk cohort included in the AMACING trial compared with the other trials conducted in high-risk groups receiving coronary intervention, it was the Work Group view that the recommendation for intravenous crystalloids for CA-AKI prophylaxis should be applied to people deemed at high risk of CA-AKI to warrant preventive intervention.

The optimal intravenous fluid type for CA-AKI prevention remains uncertain due a lack of direct comparisons. No direct trial comparisons between oral hydration versus no hydration or 0.45% sodium chloride versus no hydration were available; however, in indirect comparisons by network meta-analysis, neither oral hydration nor 0.45% saline solution significantly reduced CA-AKI compared to no hydration (Supplementary Tables S72 and S73).[625] In contrast, the network meta-analysis found lower risks of CA-AKI with

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intravenous 0.9% saline (2 trials with direct comparisons) and sodium bicarbonate (1 direct trial) versus intravenous 0.45% saline (Supplementary Tables S74 and S75).[625] Thus, for people identified at high risk of CA-AKI warranting periprocedural hydration, the Work Group deemed that these findings supported the practice of using intravenous isotonic crystalloid solutions in preference to hypotonic intravenous solutions or oral hydration.

Well-conducted RCTs, including the PRESERVE trial,[634] have demonstrated no superiority of sodium bicarbonate over 0.9% saline in preventing CA-AKI or improving kidney outcomes within 90 days (Supplementary Table S76).[615, 629, 630, 635-648] Across low- or moderate risk of bias RCTs (those without serious limitations) there is no evidence of differences in incident AKI (RR: 0.99; 95% CI: 0.88–1.13; 18 RCTs, N=10.080) or of need for RRT (RR: 1.21; 95% CI: 0.81–1.82; 16 RCTs, N=9175); although, the estimate for RRT was imprecise due to the low incidence of RRT (approximately 1.0%). As has been previously noted, high risk of bias studies favored sodium bicarbonate over 0.9% saline to prevent incident AKI.[649, 650] However, in the largest RCT, the landmark PRESERVE trial conducted in 5177 participants with CKD G3–G4 undergoing arteriography, sodium bicarbonate versus 0.9% saline did not reduce the primary endpoint of a composite of death, need for dialysis, or a persistent SCr increase of ≥50% at 90 days, nor reduce the incidence of CA-AKI.[629] Similarly, in the multicenter HYDRAREA trial involving critically ill participants, Valette *et al*. found that isotonic sodium bicarbonate did not reduce CA-AKI incidence following contrast administration compared to 0.9% saline.[630] Both solutions are generally safe, but sodium bicarbonate may carry a slightly higher risk of electrolyte disturbances, such as hypokalemia, and is more prone to compounding errors from manual preparation. Given similar effectiveness in studies without high risk of bias and a slightly more favorable safety and cost profile, 0.9% saline is often preferred in clinical practice unless specific patient factors, such as metabolic acidosis, suggest a potential advantage with administration of bicarbonate.

The optimal fluid volume and timing of administration for prevention of CA-AKI remain uncertain. In the cluster randomized Contrast RISK trial of multimodal intervention for CA-AKI prevention in coronary angiography and intervention, the hydration approach guided by LVEDP promoted use of isotonic 0.9% saline or sodium bicarbonate at 3 ml/kg for 1 h before the procedure followed by an LVEDP-guided rate during and for 4 hours post-procedure.[153] This approach resulted in a mean volume of approximately 850 ml of prophylactic isotonic crystalloid administration, and, in concert with a reduction in contrast dose, significantly reduced the incidence of CA-AKI without increasing the risk of MACE, including heart failure. A secondary analysis of intravenous crystalloid (isotonic 0.9% saline or sodium bicarbonate) administered with angiography in the PRESERVE trial suggested that a total of 1 l of crystalloid delivered over 1 hour pre-contrast to 6 hours post-contrast administration was associated with a similar risk of death, dialysis, or persistent abnormal kidney function at 90 days to larger volumes administered over longer periods.[651]

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The harms of fluid administration can include complications from volume overload such as pulmonary edema if excessive fluids are administered, which may occur in people with heart failure or compromised cardiac function. Thus, caution is warranted applying this recommendation to people with or at high risk of volume overload and people with a low risk of CA-AKI who may not benefit.

Certainty of evidence

There is high certainty of evidence that prophylactic volume expansion with intravenous isotonic crystalloid solution (versus no hydration) prior to intravascular contrast reduces the risk of incident AKI, RRT, and mortality in adults at increased risk of AKI.[625, 631, 632] Trials in children are lacking.

There is very low certainty of evidence regarding prophylactic volume expansion with either oral hydration or intravenous 0.45% saline versus no hydration. No RCTs have been found that directly compared either these interventions to no hydration. Conclusions are based on a network meta-analysis of RCTs of adults at receiving intravascular contrast; the network meta-analysis evaluated only incident AKI.[625]

There is low certainty of evidence that prophylactic volume expansion with intravenous isotonic (0.9%) saline reduces the risk of incident AKI compared with intravenous hypotonic (0.45%) saline in adults.[625] The certainty of evidence was downgraded for some methodological limitations and imprecision (since the summary estimate was near, but not statistically significant).

There is low certainty of evidence that prophylactic volume expansion with intravenous sodium bicarbonate reduces the risk of incident AKI compared with intravenous hypotonic (0.45%) saline in adults.[625] The certainty of evidence was downgraded for some methodological limitations and sparseness of data. A single study directly compared the fluid interventions, but the network meta-analysis was consistent.

There is moderate certainty of evidence that in adults at increased risk of AKI who are undergoing intravascular contrast imaging, the risk of incident AKI, and possibly RRT, is similar with prophylactic hydration with either intravenous isotonic sodium bicarbonate or 0.9% saline solutions.[615, 629, 630, 635-648, 652-665] While meta-analysis of all studies suggests a benefit for preventing AKI with sodium bicarbonate, we found that high risk of bias trials were more likely to report this finding. Our conclusion is based on sensitivity analyses excluding high risk of bias trials, which found no statistically significant difference in risk of incident AKI. For AKI, the certainty of evidence for studies with no methodological limitations (low risk of bias) was downgraded to moderate due to imprecision and the certainty of evidence for studies without serious methodological limitations (low or moderate risk of bias) was downgraded to moderate due to some methodological limitations. The

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certainty of evidence for RRT was very low due to imprecision, rare events in most studies, and methodological limitations.

Values and preferences

People at high risk of CA-AKI and healthcare professionals generally value interventions that protect kidney function without introducing significant additional risk or burden. Strategies that are simple, evidence-based, and have a favorable safety profile are preferred. Prophylactic periprocedural volume expansion with intravenous crystalloids is noninvasive, low cost, and well established in clinical practice. Preferences often lean toward 0.9% saline due to its widespread availability, lower cost, familiarity, and relative simplicity of preparation and use. People at high-risk and their healthcare professionals typically prioritize kidney protection and accept the inconvenience of fluid administration if it can meaningfully reduce the risk of CA-AKI. However, people with conditions like heart failure may place a high value on avoiding volume overload and may prefer tailored or more conservative hydration approaches. For people with or at risk of complications from volume overload, shared decision-making is important, with preferences influenced by perceived risk, severity of comorbidities, prior experiences, and trust in the recommendation of the clinical team.

Resource use and costs

Prophylactic intravenous crystalloids for people at high risk of CA-AKI is generally considered a low-cost intervention, especially when compared to the potential expenses associated with managing CA-AKI, including prolonged hospitalization, dialysis, and long-term care for CKD. The direct costs involve the solutions themselves, intravenous administration supplies, and healthcare professional time for monitoring and delivery. Saline (0.9%) is inexpensive, widely available, and already integrated into most hospital formularies and workflows, making it a low-cost and low-resource option. In contrast, isotonic sodium bicarbonate is generally more expensive and may require additional resources to support on-site compounding or special preparation. This can increase pharmacy and nursing workload and resource requirements, as well as the potential for error.

Indirect costs may arise from extended pre- or post-procedure observation, particularly in outpatient settings where additional staffing or bed occupancy is required. While the intervention is relatively inexpensive, the cost-effectiveness depends on appropriate patient selection. Targeting those at high risk of CA-AKI can avoid unnecessary resource use in people at low risk. In settings with limited capacity or staffing, such as outpatient settings, the logistics of administering fluids pre- and post-contrast may also contribute to operational strain. Overall, when used judiciously in people at high risk, prophylactic intravenous fluid administration is a resource-efficient strategy that may prevent costlier complications.

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Considerations for implementation

Implementing this recommendation requires coordination across clinical teams to identify people at high risk, and standardized protocols and infrastructure to support timely fluid administration. Key considerations include use of strategies for identifying people at high-risk using risk assessment tools. Protocols should promote the use of 0.9% saline, with guidance on rate and duration of fluid administration with adjustments for comorbidities like heart failure where fluid overload is a concern. Decision support tools that are integrated into clinical workflows in radiology, cardiology, and emergency departments may aid implementation.[153] Education and training for staff, accompanied by audit and feedback, can facilitate effective implementation. Access to day units or infusion spaces may be needed for outpatient procedures. Overall, successful implementation depends on institutional commitment, interdisciplinary collaboration, and mechanisms to monitor adherence and outcomes.

Rationale

The use of iodinated radiocontrast media has been associated with the occurrence of AKI, with varying rates reported depending on the population studied, the type, route and dose of contrast agent being used, and the presence of other risk factors for AKI. Existing data support the use of periprocedural fluid administration in people at high risk without fluid overload but there is no evidence that a particular type of fluid is superior for AKI prevention to 0.9% saline which is available worldwide. This recommendation is aligned with the joint ACR/NKF Guideline.[609] This recommendation is specific to fluid administration for CA-AKI prevention, and distinct from Recommendation 3.1.2 favoring buffered crystalloids over 0.9% saline for other patient groups at risk of AKI/AKD.

Practice Point 4.9.2.2: In the absence of volume overload, it is appropriate to hold diuretics when administering isotonic crystalloid to prevent CA-AKI in adults at high risk.

Several trials have suggested that prophylactic diuretic administration increases the incidence of CA-AKI, potentially by causing hypovolemia,[666-668] although this has been an inconsistent finding.[669] Furthermore, several trials have found that matching hydration to forced diuresis using furosemide can reduce the incidence of CA-AKI, when delivered using of an integrated device matching saline fluid replacement to urine flow rate.[625, 627]

In a recent Cochrane review, prophylactic furosemide did not decrease the incidence of CA-AKI in an analysis of 8 trials involving 1886 participants (RR: 0.87; 95% CI: 0.57–1.34, P=0.54). Findings were similar in a subanalysis of 5 of these trials (n=1604 participants) that reported RRT incidence post-contrast (RR: 0.76; 95% CI: 0.35–1.65; P=0.48).[427] This review also included trials that compared the use of furosemide together with an integrated device to match saline administration to urine flow rate versus saline alone. A total of 1302 participants were included in 2 trials of people receiving coronary

angiography, and 3 trials of transcatheter aortic valve replacement. There was no difference in CA-AKI between furosemide-forced diuresis with device-guided urine output replacement versus saline hydration (RR: 0.83; 95% CI: 0.48–1.44; P=0.51). Further, among the subgroup of 8 trials (n=930 participants) comparing furosemide *without* an integrated urine flow rate monitoring and fluid replacement device to saline hydration, the former did not significantly change the incidence of CA-AKI (RR: 0.83; 95% CI: 0.53–1.28; P=0.39).[427] However, it should be noted that the cardiac procedures across these trials were significantly heterogeneous, including 3 trials in participants having coronary angiography, 2 trials in people undergoing cardiac surgery, 1 trial using furosemide to manage volume overload in people in the ICU with respiratory failure, and a trial comparing atrial natriuretic peptide versus saline (no furosemide). Thus, a personalized approach to decisions about the use of diuretics in people at risk of CA-AKI and that the practice of withholding diuretics was rational when administering prophylactic isotonic crystalloid for volume expansion in the absence of volume overload.

4.9.3 Prophylactic therapies: Medication management

The Work Group agrees with the following practice point and radiology guideline statements related to the intravenous administration of radiocontrast from the *KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of CKD*.

Practice Point 4.9.3.1: The intravenous administration of radiocontrast media can be managed in accordance with consensus statements from the radiology societies in people with AKI or GFR <60 ml/min per 1.73 m^2 (CKD G3a–G5) undergoing elective investigation.

The Work Group refers the reader to the most recent radiology guidelines specifically noting the difference between intravenous and intra-arterial radiocontrast:

- Use of low-osmolality contrast media and iso-osmolarity contrast media
- Use of minimum radiocontrast dose to achieve a diagnostic study
- Withdrawal of nonessential potentially nephrotoxic medications (e.g., NSAIDs, diuretics, aminoglycosides, amphotericin, platins, zoledronate, and methotrexate) in people with AKI or eGFR <30 ml/min per 1.73 m^2 for 24–48 hours before and 48 hours after radiocontrast exposure
- In people with eGFR >30 ml/min per 1.73 m^2 and without evidence of AKI, metformin need not be stopped before iodinated contrast media (ICM) administration, and there is no need for testing to evaluate GFR afterward. For people with AKI or an eGFR ≤30 ml/min per 1.73 m^2, it remains appropriate to stop metformin at the time of or before ICM injection and should not be restarted for at least 48 hours and only then if GFR remains stable and the ongoing use of metformin has been reassessed by the clinical team.[670]
- Consideration of avoiding dehydration for people not undergoing dialysis and who have eGFR <30 ml/min per 1.73 m^2 or AKI and receiving intravenous contrast.[671, 672]

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- Use of N-acetylcysteine, ascorbic acid, furosemide, dopamine, fenoldopam, or calcium channel blockers as preventative measures of CA-AKI has not been shown to be a consistent benefit.[610]
- Prophylactic pericontrast hemodialysis has been shown to be potentially harmful and is not recommended.[610]

Recommendation 4.9.3.1: We suggest not routinely withholding renin-angiotensin system inhibitors (RASi) before procedures with iodinated radiocontrast administration in adults (*2C*).

This recommendation places a high value on evidence synthesis of RCTs that have not demonstrated significant differences in CA-AKI risk between the strategies of withholding or continuing RASi in the periprocedural period for radiocontrast procedures. A systematic review of 4 RCTs found no significant difference in CA-AKI incidence following temporary ACEi or ARBs discontinuation versus continuation in participants undergoing elective coronary angiography. This recommendation also places value on the potential harms of inappropriate RASi withdrawal and medication errors that may result from the practice of routine withdrawal.

Key information

Balance of benefits and harms

Four trials of withholding RASi were identified, including a total of 2042 participants who underwent elective coronary angiography and/or a PCI with contrast (Supplementary Table S77).[673-676] There was no significant difference in CA-AKI incidence following temporary ACEi or ARB discontinuation versus continuation in participants undergoing elective coronary angiography (OR: 0.76; 95% CI: 0.48–1.19). Given the lack of precision in the effect estimate, this result does not exclude the potential of a small reduction in CA-AKI with ACEi or ARB withdrawal. However, potential harms may result from RASi withdrawal, including exacerbation of heart failure, and medication management errors resulting in failure to resume these medications for people with guideline recommended indications, such as heart failure, diabetes, and CKD. However, the trials were generally underpowered to detect significant differences in harms. It may be appropriate to withhold RASi during peri-procedural management of adverse events such as hypotension, hyperkalemia, and AKI, which requires an individualized rather than systematic approach. When RASi are withheld due to short term periprocedural adverse events, healthcare professionals should reassess the appropriateness of resuming treatment and restarting these agents, when possible, to improve long-term outcomes.

Certainty of evidence

There is low certainty of evidence that, in adults receiving intravascular contrast for cardiac procedures, there are not differences in incident AKI whether RASi are withheld or not, with no evidence of differences for other benefits or harms.[673-676] For incident AKI, the

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certainty of evidence was downgraded for methodologic limitations of the studies and for imprecision. For most other critical outcomes, including poor control of underlying differences due to withholding RASi, events were rare resulting in imprecise or very imprecise estimates.

Values and preferences

Patient and healthcare professional values and preferences typically focus on minimizing the risk of AKI while maintaining stable control of chronic conditions like hypertension, heart failure, or CKD. Many people prioritize avoiding CA-AKI, especially if they have preexisting abnormal kidney function, and may be open to temporarily stopping medications if it is clearly explained as a precautionary measure. However, others may be concerned about destabilizing their BP or worsening heart failure symptoms, particularly if they have experienced complications from medication changes in the past. Patients also tend to prefer clear, individualized guidance from their healthcare team, rather than routine or automatic discontinuation of important long-term medications. Overall, preferences often lean toward a personalized approach that balances potential kidney risks against the importance of maintaining cardiovascular and hemodynamic stability with decisions made in collaboration with trusted healthcare professionals.

Resource use and costs

Withholding RASi incurs minimal direct costs, as it primarily involves clinical decision-making and patient counseling rather than additional medications or interventions. However, indirect resource use can arise from the need for preprocedural medication reviews, coordination among specialists (e.g., cardiology, nephrology, radiology), and follow-up to reassess and restart therapy post-procedure. In some cases, discontinuation may lead to adverse events such as uncontrolled hypertension, fluid retention, or heart failure exacerbations, which can result in increased healthcare utilization, including emergency visits or hospital admissions. Additionally, system-level protocols or electronic alerts may be required to standardize the withholding and reinitiation process, adding to administrative and information technology resource demands. Therefore, while the act of withholding RASi is low-cost, the broader resource implications depend on the infrastructure needed to support this practice.

Considerations for implementation

Implementing this strategy requires careful consideration of patient selection, workflow integration, and communication across healthcare teams. A key challenge is identifying which people might benefit from temporary RASi discontinuation, as the evidence supporting routine withholding is uncertain and the risk-benefit balance varies by individual factors such as baseline kidney function, cardiovascular and volume status. Clear protocols and decision-support tools may help to guide healthcare professionals, but rigid implementation could lead to inappropriate discontinuation in people for whom these medications are critical for managing heart failure or hypertension. Effective implementation

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also requires timely medication reconciliation, patient education about holding and restarting the drugs, and coordination between procedural teams, primary care, and specialists. Without such systems in place, there is a risk of miscommunication, prolonged interruption of therapy, or adverse clinical outcomes. As such, a flexible, patient-centered approach with clinical judgment is essential for safe and effective implementation.

Rationale

The routine withholding of RASi such as ACEi or ARBs before exposure to iodinated radiocontrast has been proposed as a strategy to reduce the risk of CA-AKI, based on the theoretical concern that these medications may impair kidney autoregulation and exacerbate contrast-induced nephrotoxicity. However, overall, evidence does not support a clinical benefit from withholding RASi. While temporary discontinuation may modestly reduce the risk of transient declines in kidney function in some people at high risk, it also carries potential harm, including loss of BP control, exacerbation of heart failure, and interruption of cardiovascular or kidney protection in people with chronic conditions. The balance of benefits and harms therefore depends on individual risk factors, such as baseline kidney function, volume status, and cardiovascular stability, supporting a more individualized approach rather than a standard policy of withholding RASi before contrast exposure.

Accordingly, the Work Group suggested against routine withdrawal of these drugs before elective contrast imaging procedures, due to lack of evidence for benefit with this strategy and risk of potential harms if broadly applied. This suggestion differs from statements to hold RASi before elective CT scans in people at risk of CA-AKI provided by the ACR/NKF Guidelines and included within Practice Point 4.4.1.2 in *KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of CKD*.[17, 609]

4.10 Temporary withdrawal of medications to prevent AKI during major surgery

Recommendation 4.10.1: We suggest not routinely withholding renin-angiotensin system inhibitors (RASi) to prevent AKI in adults having elective major cardiac *(2D)* or non-cardiac surgery *(2B)*.

This recommendation places a high value on evidence-based strategies to reduce the risk of AKI and related perioperative complications following cardiac surgeries. There is evidence that use of RASi increases the risk of hypotension, but there is no evidence that their use significantly increases the risk of major perioperative complications or AKI following major non-cardiac surgery. The effects of RASi use on AKI following cardiac surgery are uncertain. This recommendation places value on the potential harms of inappropriate RASi withdrawal that may result from a strategy of routine withdrawal and highlights the need for individualized decision-making and management.

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Key information

Balance of benefits and harms

Use of RASi in the perioperative period has the potential to impair renal autoregulation and contribute to hypotension during anesthesia. RCTs have shown a higher risk of perioperative hypotension in adults who continue versus stop RASi before major elective non-cardiac surgery; however, these trials have not demonstrated a reduction in incidence of AKI risk when these agents are held preoperatively. The benefits of withholding RASi to avoid perioperative hypotension must be carefully weighed against the potential harms of discontinuation, including exacerbation of underlying conditions such as heart failure or uncontrolled hypertension, and the risk of rebound hypertension. Thus, decisions regarding RASi withholding should be individualized, balancing patient-specific cardiovascular risks against potential kidney benefits, ideally guided by multidisciplinary perioperative planning.

Major surgery can be defined as surgery with an expected duration >2 hours from the surgical incision, and a post-operative hospital stay of ≥3 days.[677] A systematic review, with 16 studies of perioperative ACEi or ARB cessation around elective major non-cardiac surgeries included 8 RCTs that enrolled over 8000 subjects (Supplementarty Table S78).[678] Although hypotension in the intraoperative and post-operative period was more common among people continuing ACEi or ARB therapy compared to those withholding them, mortality and major post-operative complications were no different with continuing versus stopping RASi. In 2 RCTs (n=2476 participants) that included AKI as an outcome, the incidence of AKI was not increased in the group that received perioperative RASi (OR: 1.01; 95% CI: 0.78–1.30) (Supplementary Table S78).[678] Specifically, AKI incidence was 11% in both groups in the "STOP or not STOP" trial by Legrand et al., and 10% in both groups in the Strategies for Prescribing Analgesics Comparative Effectiveness (SPACE) trial.[679] Further, a published a prespecified secondary analysis of the PeriOperative ISchemic Evaluation-3 (POISE-3) trial, a partial factorial RCT, compared a "hypotension avoidance strategy" in which RASi were replaced with alternative antihypertensive agents in the protocol versus a "hypertensive avoidance strategy" that continued usual antihypertensives including RASi during major non-cardiac surgery.[408] Although less intraoperative hypotension was reported in the hypotension avoidance group, the incidence of AKI did not differ between these groups (15.1% vs. 14.4%, RR: 1.05; 95% CI: 0.93–1.19), including among subgroups with CKD .

It is uncertain based on current evidence whether continuing RASi perioperatively during cardiac surgery is beneficial or harmful. The current literature has predominantly included observational studies (Supplementary Table S79),[680-682] and there has only been a single RCT comparing temporary withdrawal versus continuation of RASi during cardiac surgery that was underpowered for AKI-related outcomes.[683]

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Certainty of evidence

There is moderate certainty of evidence that temporarily withdrawing RASi prior to elective major non-cardiac surgery in adults does not alter the risk of AKI, but also without evidence of increased risk of poor cardiac outcomes.[678] The certainty of evidence for AKI-related outcomes was downgraded due to imprecision. The certainty of evidence related to poor control of underlying cardiac conditions was further downgraded due to some inconsistency, imprecision, and sparse data for some events.

There is very low certainty of evidence, from 1 small trial, that temporarily withdrawing RASi prior to elective cardiac surgery (elective or urgent coronary artery bypass graft and/or valve surgery) in adults does not alter the risk of AKI-related outcomes or death, but also without evidence of increased risk of poor cardiac outcomes.[683] The certainty of evidence was downgraded for some methodological limitations, sparse evidence, and highly imprecise estimates.

Values and preferences

Many people value the avoidance of serious complications like AKI, especially if it could lead to prolonged hospitalization, dialysis, or CKD. As such, they may be willing to temporarily withhold a familiar medication if there is a reasonable chance of reducing this risk. However, people with conditions like heart failure or poorly controlled hypertension may place a higher value on cardiovascular stability and continuity of therapy, expressing concern about potential decompensation if RASi are withheld. Healthcare professionals, meanwhile, must balance these patient preferences with clinical evidence, often erring on the side of caution in stopping RASi in high-risk surgeries or in those with labile BP. Shared decision-making, guided by a clear explanation of the potential risks and benefits, is crucial to aligning treatment decisions with individual patient values.

Resource use and costs

Withholding RASi prior to major surgery involves relatively low direct costs, as it typically requires only temporary discontinuation without the need for substitute medications. However, the broader resource implications can vary. If withholding these agents reduces the incidence of perioperative hypotension, this may lead to cost savings by preventing complications such as AKI that require extended hospital stays, intensive monitoring, or interventions like dialysis. On the other hand, if discontinuation leads to decompensated heart failure, severe hypertension, or other cardiovascular complications, this could increase healthcare utilization and associated costs. Additional resources may also be needed for preoperative assessment, patient counseling, and post-operative monitoring to manage the risks of withholding therapy. Overall, while the act of withholding is inexpensive, its downstream effects on resource use and cost are highly dependent on individual patient risk profiles and surgical complexity.

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Considerations for implementation

Implementing a strategy to withhold RASi before major surgery requires careful coordination across the perioperative care team, including surgeons, anesthesiologists, internists, and pharmacists. Clear protocols should be established to identify which people are appropriate candidates for temporary discontinuation, typically those undergoing high-risk surgeries or with elevated AKI risk, while ensuring that those with contraindications to withholding, such as heart failure or poorly controlled hypertension, are appropriately managed. Timing is also critical; RASi are generally withheld 24 hours prior to surgery, and plans must be in place for timely reinitiation post-operatively based on hemodynamic stability and kidney function. Patient education is another key component, as people must understand the rationale for withholding medications, they may have been taking long-term. Implementation may be facilitated by clinical decision support tools within electronic medical records to prompt appropriate withholding and follow-up, minimizing variability in practice and supporting safe, individualized care.

Rationale

Current evidence does not support a routine strategy of withholding RASi perioperatively during major non-cardiac or cardiac surgeries to reduce the incidence of post-operative AKI. However, surgical and anesthetic teams may choose to withhold RASi to minimize the development and severity of perioperative hypotension by avoiding drug-induced vasoplegia, thus reducing increased fluid and vasopressor requirements, and other complications. These considerations may be more clinically relevant in people undergoing emergency surgeries, particularly in people who are hemodynamically unstable, have evolving AKI, or are developing hyperkalemia. Decision making may also differ for people with reduced heart function. Finally, if these drugs are held for reversible periprocedural adverse events (AKI, hyperkalemia, hypotension, and hyperkalemia), RASi should be restarted, when possible, to improve long-term outcomes.

4.11 Medication management during intercurrent illness or "sick day protocols"

Recommendation 4.11.1: We suggest temporarily stopping specific classes of drugs in the context of acute illnesses that predispose to volume depletion, to prevent AKI caused by hypovolemia (*2D*).

The Work Group also agrees with the following practice point from Section 4.3 of the *KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of CKD* and believe it also applies to people with AKI or AKD:[17]

Practice Point 4.11.1: If medications are discontinued during an acute illness, communicate a clear plan of when to restart the discontinued medications to the affected person and healthcare professionals, and ensure documentation in the medical record.

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This recommendation places a high value on strategies that can mitigate the adverse effects of specific medications during acute illnesses that result in hypovolemia and reduced GFR. RASi, diuretics, and NSAIDs can exacerbate volume depletion, reduce eGFR, and contribute to the development of AKI. There is also a risk of adverse events from hypoglycemic agents such as sulfonylureas and metformin when GFR declines. It is therefore rational to temporarily stop these medications during an acute illness that can lead to AKI. This recommendation acknowledges there is a lack of evidence of effective implementation strategies for "sick-day protocols" and potential harms of inappropriate medication self-management. Individualized decision-making, patient counselling, and self-management strategies are required to implement this recommendation.

Key information

Balance of benefits and harms

Temporarily stopping certain classes of medications during an acute illness that predisposes to volume depletion (such as vomiting, diarrhea, or febrile illnesses) may help to prevent AKI caused by hypovolemia. Medications commonly held in this context include RASi diuretics, NSAIDs, and metformin, often referred to as part of a "sick day" protocol. The benefit of this approach lies in reducing the risk of further compromising renal perfusion or exacerbating volume depletion, which can precipitate or worsen AKI. However, there are potential harms associated with this strategy. Interrupting these medications, particularly in people with heart failure, diabetes, hypertension, or CKD may lead to destabilization of chronic conditions, resulting in uncontrolled hypertension, hyperglycemia, or fluid overload. Moreover, unclear instructions or inconsistent messaging may lead to inappropriate discontinuation or delays in restarting therapy, potentially increasing the risk of adverse outcomes. Therefore, while withholding these drugs during acute volume-depleting illnesses may protect kidney function, it must be balanced with careful patient education, individualized risk assessment, and close follow-up to ensure timely reinitiation once the acute illness resolves.

Our systematic review of the use of "sick-day protocols" identified only 1 RCT that evaluated the effect of an intervention to implement "sick day rules" on the outcome of AKI (Supplementary Table S80).[684] This 6-month trial followed 280 adults with CKD G3–G5 receiving a diuretic, RASi, NSAID, or metformin to management with a sick day protocol versus standard management.[684] The primary endpoint of eGFR change after 6 months did not differ between groups nor was there any difference in the very low incidence of AKI or hospitalization over this short follow-up period. Notably, usability testing of the sick-day protocol revealed frequent errors in protocol use and a high rate of failure by participants in identifying the correct medications to be withheld. This highlights safety concerns for patient self-management, including the risk of applying sick-day protocols to inappropriately classified illnesses, such as heart failure, where holding medications might be deleterious. Our systematic review also identified 6 trials that evaluated withholding RASi in people with acute COVID-19 (Supplementary Table S81).[685-689] In these trials, withholding versus

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continuation of RASi similarly failed to demonstrate effects on AKI-related events, mortality, or other clinical endpoints; although, estimates were mostly very imprecise due to rare events.

Certainty of evidence

There is very low certainty of evidence that stopping various medications in adults with acute illnesses or COVID-19 does not affect the risk of AKI but may increase the risk of unplanned hospital admissions.[684,685-689] Evaluated medications included RASi, loop, or thiazide diuretics, mineralocorticoid receptor antagonists, metformin, and NSAIDs. The evidence for non-COVID-19 illnesses is based on a single study, which was downgraded for methodological limitations, imprecision, and sparse data. The evidence for COVID-19 was downgraded primarily for highly imprecise estimates of effect for AKI-related outcomes and for some methodological limitations and inconsistent findings.

Values and preferences

People generally prioritize avoiding serious complications such as AKI, particularly if they understand the potential for long-term consequences like CKD or dialysis. Many are willing to make changes to their medications temporarily if clearly advised that doing so can prevent harm during periods of acute illness. However, people with chronic conditions such as heart failure, hypertension, diabetes, or CKD may also value stability and continuity in managing these conditions and may feel anxious about stopping medications they have been counselled to take regularly. Preferences may vary based on past experiences, health literacy, and trust in their healthcare professionals. Healthcare professionals must consider these factors and engage in shared decision-making, providing clear, personalized guidance on when and how to pause and resume medications, to align care with an individual patient's values, goals, and understanding of risk.

Resource use and costs

Temporarily stopping medications is a low-cost intervention in itself; however, effective implementation may incur indirect costs related to the patient education, clinical monitoring, and follow-up care required. Resources are needed to ensure people understand when and which medications to pause, including healthcare professional time, educational materials, or decision-support tools. Inadequate communication can lead to inappropriate discontinuation or failure to restart therapy, potentially resulting in increased healthcare utilization due to poorly controlled chronic conditions or adverse drug events. On the other hand, by preventing episodes of AKI, temporary drug cessation may reduce hospital admissions, diagnostic testing, and long-term complications, offering potential cost savings to the healthcare system. Overall, while the intervention is simple and inexpensive, its cost-effectiveness depends on coordinated implementation and effective self-management when attempted in community settings.

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Considerations for implementation

Key considerations for implementation include identifying which medications should be paused and establishing clear criteria for when to withhold and restart them. Research suggests that errors in implementing sick day guidance protocols are frequent. Successful implementation depends heavily on patient education and empowerment, as people must be able to recognize symptoms of volume depletion (e.g., vomiting, diarrhea, fever) and understand how to respond appropriately. Healthcare professionals must ensure consistent messaging across care settings, which can be supported by integrating "sick day rules" into routine care through printed materials, pharmacist counseling, and digital health tools. Attention is needed for high-risk populations, such as older adults or those with cognitive impairments, who may require caregiver involvement. Additionally, systems should be in place for timely follow-up to reassess medication needs once the acute illness resolves, minimizing the risk of inappropriate drug dosing or prolonged treatment interruption.

The PAUSE Preventing Medication Complications During Acute Illness Through Symptom Evaluation and Sick Day Guidance (PAUSE) Medication Safety Advisory Panel developed consensus-based recommendations for sick day medication guidance (SDMG) through a Delphi process. These recommendations (with a ≥80% voter rating in the Delphi survey) are provided in Table 40 and highlight that SDMG should focus on patient, or caregiver for children, self-management in conjunction with support from their healthcare professional.[690]

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Table 40 | Sick day medication guidance for adults

Triggers to initiate sick day medication guidance:

- Vomiting or diarrhea, resulting in significant fluid losses
- Anorexia or nausea, resulting in significant decrease in fluid intake
- New light-headedness, dizziness, or fainting, particularly with sitting or standing up
- Decreased weight (3 kg in 2 days)
- Decreased urine output

When self-management is appropriate:

- There is an absence of severe symptoms
- Patients (and carers) feel they can cope
- Patients can keep up with their fluid intake

Medications that should be temporarily stopped (until symptoms are resolved or up to 3 days, whichever is earliest):

- Angiotensin-converting enzyme inhibitors (ACEi)/angiotensin II receptor blockers (ARBs)
- Loop diuretics
- Thiazides/thiazide-like diuretics
- Potassium-sparing diuretics
- Sodium-glucose cotransporter-2 inhibitors
- Nonsteroidal anti-inflammatory drugs
- Metformin
- If blood glucose is low, hold insulin/sulfonylurea/meglitinide until blood glucose recovers
- If blood glucose is more elevated than usual, empirical 10%–20% increase in basal and bolus insulin doses (if unsuccessful at lowering blood glucose, contact healthcare professional)
- Angiotensin receptor neprilysin inhibitors
- Direct rein inhibitors

When assistance/support from healthcare professional should be sought:

- Patients feel they are not coping
- Signs and symptoms have not resolved within 72 hours
- Patients cannot keep up with intake of foods or fluids
- Patients have recurrent low blood glucose readings
- Patients experience significant increase in blood glucose not coming down with self-adjustment after 24 hours

Adapted from Watson *et al*.[690]

Rationale

The Work Group supports the position that "sick day protocols" that involve temporarily withholding select medications can be a useful approach,[690] as discussed in Section 4.3 of the *KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of CKD*.[17] This may be applied to appropriately selected people with chronic conditions treated with the following medications: sulfonylureas, ACEi, diuretics, direct renin inhibitors, metformin, ARBs, NSAIDs, and SGLT2i (often described with the acronym "SADMANS").[691] However, there is a paucity of evidence of strategies to implement sick day protocols effectively,[684, 687-689] and there are significant safety concerns with previously described approaches. Healthcare professionals should ensure consistent education and messaging across care settings and provide adequate self-management support through printed materials, pharmacist counselling, and digital health tools. Caution applying self-management strategies is warranted in younger or older people and those with cognitive

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impairment, who may require caregiver involvement. Mechanisms should be in place for timely follow-up to support people making medication changes, including resuming medications appropriately once the acute illness resolves.

There is potential for harm if people make mistakes in recognizing an acute illness associated with risk of volume depletion, identifying which drugs are appropriate to stop , and when to restart them.[692] A failure to restart appropriate medications is a commonly reported problem. Accordingly, the Work Group endorses Practice Point 4.3.2 from the *KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of CKD* repeated above[17] emphasizing that a plan to restart medications that have been temporarily discontinued should be clearly communicated to patients and other healthcare professionals. Documentation of this plan in the medical record may improve consistency and continuity of care. Patients may additionally benefit from medication review within a month to ensure appropriate medications are restarted at the correct dose.

4.12. Considerations specific to children

4.12.1 Biomarker characterization of drug-related AKI

Practice Point 4.12.1.1: Urine biomarkers of kidney damage can be helpful in detecting nephrotoxin-associated AKI in newborns..

Kidney damage biomarkers may help in identifying AKI in neonates exposed to multiple nephrotoxic drugs.[693] Urinary NGAL can be utilized for AKI detection without the need for blood draws which contribute to neonatal anemia. It also avoids the interference of maternal SCr on AKI detection. The negative predictive value of a urine NGAL value ≤250 ng/ml was 96.8% (95% CI: 93.3%–100%) and urine NGAL ≥400 ng/ml demonstrated a positive likelihood ratio of 2.76 (95% CI: 1.39–4.13) when compared against daily SCr testing in neonates exposed to nephrotoxic drugs. This suggests that urine NGAL may have a role for detection in drug-related AKI in neonates, replacing blood draws in those exposed to nephrotoxic medications. However, more research is needed and the ideal urine NGAL thresholds require further validation.[694]

4.12.2. Management of drugs eliminated by the kidney

Practice Point 4.12.2.1: Trends in SCr and urine output can be used to guide dosing of drugs excreted by the kidney. The validity of KeGFR equations to inform drug dosing in children is uncertain.

Like in adults, the GFR estimating equations developed for children with CKD are unreliable in AKI because they assume a steady state of SCr. Similar to equations in adults, these formulas will overestimate GFR when SCr is rising and underestimate GFR when SCr is falling. For children with AKI, it is important to consider trends in SCr and urine output when dosing drugs excreted by the kidney. There is a lack of data on the utility of KeGFR equations for drug dosing in the pediatric population. Until more evidence is available,

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healthcare professionals should exercise caution and adjust dosing based on clinical response and drug levels when possible.

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CHAPTER 5. RENAL REPLACEMENT THERAPY

5.1. Starting renal replacement therapy (RRT)

RRT is an important kidney and organ support intervention for patients with AKI in modern clinical care. RRT may be required in a substantial proportion of acutely ill patients with AKI, depending on the population-at-risk and clinical context (e.g., septic shock, liver failure, cardiogenic shock).[695] Recent trends show increasing utilization, particularly in high-resource settings.[696, 697] Decisions to start and discontinue RRT in acutely ill patients with AKI are complex and influenced by a range of issues, including overall prognosis (i.e., potential for survival, resolution of acute illness, and RRT independence), the relative balance of risks to benefits, the availability of suitable expertise and resources, and patient preferences (Figure 14).[528]

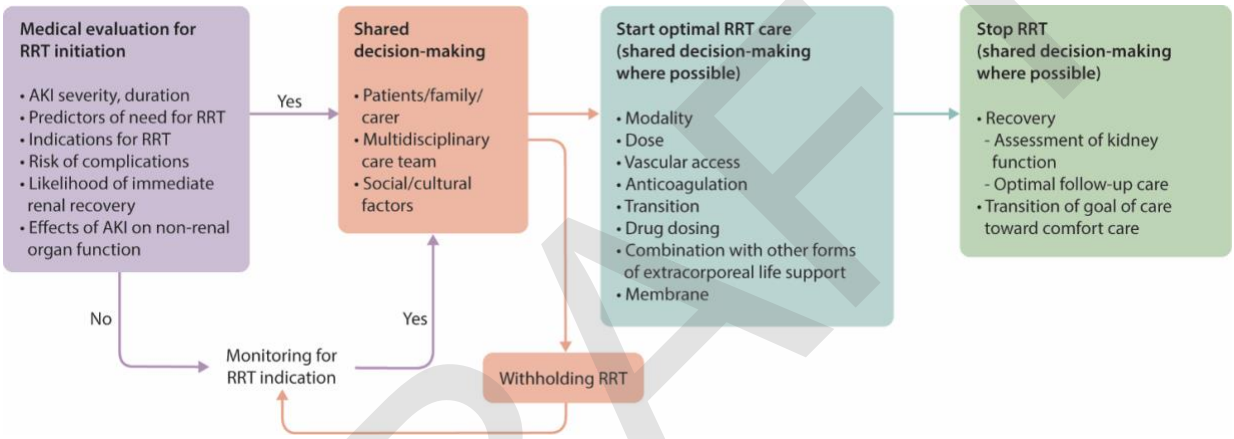

Figure 14 | Schematic diagram of RRT continuum. RRT, renal replacement therapy. Adapted from Ostermann *et al*.[528]

Practice Point 5.1.1: For children and adults with AKI, a process of informed shared decision-making should be used with patients, family, caregivers, and healthcare professionals on the relative merit and risk of treatment with RRT.

An essential consideration for treatment with RRT is the tailoring of decisions based on the values and preferences of patients and/or surrogate decision makers (e.g., family, caregiver) through an engaged process of informed, ethically acceptable, shared decision-making.[698] Shared decision-making can be defined as "a collaborative process that allows patients, or their surrogates, and clinicians to make health care decisions together, taking into account the best scientific evidence available, as well as the patient's values, goals, and preferences".[698]

Shared decision-making is widely endorsed by numerous health care organizations, including critical care and nephrology.[698, 699] Patients/surrogate decision-makers report greater satisfaction with care when confronted with transparent, consistent, and frequent

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opportunities to communicate and share in the creation of the care plan with the healthcare team.[700] Shared decision-making can provide greater clarity on the direction of care.[701, 702] In selected circumstances, this may include foregoing RRT or escalations in care.[703, 704] Provision of short-term RRT when benefits are uncertain may involve a time-limited-trial, to build trust with the patient and/or surrogate decision-makers, strengthen prognostic certainty, and shape consensus on decision-making for a care plan.[705, 706] Time-limited trials can facilitate a process of shared decision-making and have been shown to improve the quality of family meetings and reduce resource use, including RRT.[707]

While RRT can be life-sustaining for patients suffering complications of AKI, access to RRT services can be a challenge, particularly in low-resource settings. Barriers to RRT include disparate hospital resources, geographic remoteness to a center with dialysis services, and patient-incurred costs (i.e., inability to pay for any or a sustained period of dialysis). Similarly, women are disproportionately less likely to access and receive RRT, especially in low- and middle-resource settings.[708, 709] In sub-Saharan Africa, mortality of children and adults with AKI and indications for RRT but no access (i.e., did not receive) was reportedly 72%–79% and 86%, respectively, far in excess of the observed mortality of 24%–31% and 32%–31%% when RRT was available.[709]

There are numerous validated decision-making strategies (i.e., approaches; tools) that are available and that can be adapted to facilitate complex decision-making around the provision of RRT.[698] The use of decision-making algorithms may improve consistency and standardization of approaches and facilitate a framework for shared decision-making.[154, 710] Key aspects of such a framework broadly include; i) clarifying available treatment options, ii) weighing the relative risks and benefits, iii) understanding individual patient values and preferences, and iv) articulating a schedule to engage in partnered decision-making with the healthcare team.[710]

Recommendation 5.1.1: For adults with AKI, we recommend a strategy of deferred timing of RRT initiation as preferred over a strategy of early (pre-emptive) RRT initiation (*1C*).

This recommendation places a high value on avoiding the potentially unnecessary burden, resource use and costs, and potential harms associated with earlier initiation of RRT. There is low overall certainty of evidence of no differences in mortality, long-term RRT dependency, or other serious harms with deferred versus early RRT initiation in adults with AKI. A deferred RRT initiation strategy is based on the emergence of clinical indications for RRT (medically refractory metabolic or volume-related complications of AKI), rather than relying solely on creatinine or urine output-based criteria (Table 41). Deferred RRT initiation requires the capacity for prompt RRT initiation when indicated, and healthcare professionals should be mindful of local logistical factors when considering RRT timing.

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Key information

Balance of benefits and harms

All forms of RRT are invasive organ support interventions that carry inherent risks, which may increase with prolonged use. These complications can arise from the insertion and ongoing maintenance of dialysis catheters (e.g., bloodstream infection, peritoneal infection), therapy-specific adverse events (e.g., bleeding, hemodynamic instability, arrhythmias, electrolyte abnormalities), and long-term adverse outcomes (e.g., delayed or nonresolution of AKI).

The timing of starting RRT in the absence of conventional indications for RRT has long presented a central dilemma for healthcare professionals (Table 41; Figure 14) and been the focus of several RCTs in acutely ill adults.[124, 128, 711-713] In these RCTs, acutely ill adults with Stage 2–3 AKI and no conventional indications (e.g., metabolic, toxic or fluid-related complications) were allocated to an early ("accelerated" or "pre-emptive") or a deferred ("standard" or "delayed") strategy for starting RRT.

Deferred RRT initiation involves waiting until patients have medically refractory complications or persistent Stage 2 or 3 AKI exceeding 48–72 hours. Most recent large multicenter RCTs in adults have largely aligned around this definition of deferred RRT initiation (alternatively termed delayed, late, or standard initiation),[124, 712-714] however, there has been some variation.[128] This variation can present challenges when interpretating the evidence across trials and applying it to individual patients. For example, of the 231 participants in the Early vs. Delayed Initiation of Renal Replacement Therapy in Critically Ill Patients with Acute Kidney Injury (ELAIN) trial, 46.8% were enrolled after having undergone cardiac surgery.[128] AKI after cardiac surgery is common and may be associated with a unique pathophysiology and constellation of complications when compared with other groups of patients with AKI.[715] This may include nuanced differences in the capacity to tolerate complications related to AKI (e.g., fluid accumulation in the setting of reduced heart function, electrolyte/metabolic abnormalities in a setting of increased risk of arrhythmias). Systematic reviews have focused on synthesizing evidence on timing of initiation of RRT in participants after cardiac surgery.[716, 717] These have included relatively few RCTs[128, 718, 719] and observational studies with high risk of bias.[720-724] While pooled analysis implied there may be benefit to earlier RRT initiation in participants after cardiac surgery with AKI, this evidence has very-low to low certainty.

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Table 41 | Summary of indications for starting RRT in adults with AKI when implementing a deferred RRT initiation strategy.

Urgent indications (in the absence of contraindications to RRT)	• Severe hyperkalemia (K^+ ≥6.0 mmol/l, rapidly rising, or cardiac toxicity) refractory to medical therapy • Severe acidemia or metabolic acidosis (pH ≤7.2 or serum bicarbonate ≤12 mmol/l despite normal or low arterial pCO_2) refractory to medical therapy • Severe hypoxemia and perception of volume overload (diuretic-resistant pulmonary edema) • Excessive fluid accumulation refractory to medical intervention • Uremic complications (bleeding, pericarditis, encephalopathy) • Severe hyperammonemia (inborn errors of metabolisms, liver failure) • Severe intoxication with a dialyzable drug or toxin (salicylates, lithium, toxic alcohols, metformin)
Relative indications (in the absence of urgent indications of AKI)	• Persistent severe AKI (KDIGO Stage 3 ± prolonged oligoanuria) • Severe non-kidney organ dysfunction exacerbated by AKI • Severe or worsening illness acuity and trajectory • Anticipated solute burden (tumor lysis syndrome; rhabdomyolysis; intravascular hemolysis) • Limited physiological reserve to tolerate the consequences of AKI (i.e., demand-supply mismatch, severe non-kidney comorbidities) • Inability to provide target nutritional support due to fluid restriction
Relative contraindications	• Low likelihood for benefit (futile prognosis) • Receiving palliative care and/or approaching end-of-life • High likelihood of non-recovery of kidney function in patients who are not long-term dialysis candidates

Adapted from Ostermann *et al.*[725] AKI, acute kidney injury; CKD, chronic kidney disease; ICU, intensive care unit; KDIGO, Kidney Disease: Improving Global Outcomes; pCO2, partial pressure of carbon dioxide; RRT, renal replacement therapy.

No differences in 90-day mortality, 90-day dialysis dependency, length of stay (ICU and hospital), and serious adverse events were found between early versus deferred RRT initiation (Supplementary Table S82).[125, 726-728] This finding would imply that a deferred strategy to starting RRT, characterized as a "watch and wait" strategy, where RRT is delayed until confronted with worsening, persistent or medically refractory complications of AKI in acutely ill patients, can be recommended as the default standard.

In a substantial proportion of those participants allocated to the strategy of deferred RRT initiation across these RCTs, RRT was not started (range 10%–49%), due either to kidney recovery or death, potentially contributing to lower resource use and costs of care.[124, 128, 712, 713] However, in the Initiation of Dialysis Early Versus Delayed in the Intensive Care Unit (IDEAL-ICU) trial, 17% of participants with septic shock allocated to the deferred RRT

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initiation strategy did receive emergent RRT for medically refractory complications within 48 hours of randomization.[124] This observation reinforces the need for regular reassessment of the patients and also the further need for development and validation of clinical risk prediction tools (e.g., diagnostic tests, dynamic assessments, etc.) to improve real-time identification of patients most likely to derive benefit from starting RRT earlier.[171, 180, 729]

It is further plausible that accumulation and persistence of AKI-related complications may exert the risk for adverse outcomes.[730] In the Artificial Kidney Initiation for Kidney Injury 2 (AKIKI-2) trial, acutely ill participants with persistent Stage 3 AKI without urgent RRT indications were allocated to either start RRT immediately (aligned with the "delayed" strategy in the Artificial Kidney Initiation in Kidney Injury [AKIKI] trial) or further deferral ("more-delayed"), starting RRT only for a serum urea >50 mmol/l or an urgent conventional indication.[125] While there was no difference in the number of RRT-free days at 28 days between the groups (12 days for delayed vs. 10 days for more-delayed, *P*=0.93), in a prespecified analysis, 60-day mortality was higher in the more-delayed strategy compared to the delayed-strategy (55% for more-delayed vs. 44% for delayed; adjusted HR: 1.65; 95% CI: 1.09–2.50; *P*=0.07; Supplementary Table S83).[125] In addition, participants who were in a coma at randomization had a lower chance of transitioning from coma to awakening and remained comatose for longer.[731] These findings support the concept that prolonged delays should be avoided within a deferred RRT initiation strategy.

Individual studies provide further insights not captured in the formal syntheses. In the AKIKI trial, the earlier RRT initiation strategy conferred a higher risk of catheter-related bloodstream infections compared with a standard RRT initiation strategy (10% vs. 5%, *P*=0.03).[712] In the Standard (deferred) versus Accelerated (early) Initiation of Renal-Replacement Therapy in Acute Kidney Injury (STARRT-AKI) trial, more people receiving the earlier RRT initiation strategy experienced adverse events (23.0% vs. 16.5%, *P*<0.001), including hemodynamic instability and electrolyte abnormalities (e.g., hypophosphatemia).

Finally, there may be important differences between specific groups of patients that have not been the specific focus or have been underrepresented in RCTs (e.g., neonates/children[732]; cardiogenic shock[733]; solid-organ transplantation[734, 735]; extracorporeal life support [ECLS][736]), where there may be differences in the development of medically refractory complications, differences in tolerating these complications, and/or differences in relative indications for starting RRT and potential benefits with early or deferred initiation.

Certainty of evidence

The certainty of evidence in adults for the comparison of early versus standard (or delayed) RRT is low.[125, 726-728] The certainty of evidence was downgraded for imprecision across outcomes, with inconsistency across studies pertaining to mortality and reporting issues pertaining to adverse events, with sparse data for several outcomes.

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One trial with methodological concerns provided very low certainty of evidence for comparison of delayed (standard) versus more-delayed (very late) RRT.[125, 726-728] The trial had mostly very imprecise estimates of effect, but did find a significantly higher risk of death with more-delayed RRT.

Values and preferences

Survivors of critical illness treated with RRT report impaired quality-of-life (QoL) and function (e.g., new or worsened disability).[737-740] This recommendation placed high value on the potential for avoidance of RRT when applicable.

Resource use and costs

RRT represents an escalation in the complexity of care and is both resource intensive and costly.[741] In many low-resource settings, receipt of RRT is paid out-of-pocket, putting patients at risk of accelerated economic decline. A deferred strategy for RRT initiation may translate into a meaningful proportion of people with moderate-to-severe AKI averting use of RRT and lead to concomitant reductions in resource use and costs.[742]

Considerations for implementation

The adoption of a deferred strategy for RRT initiation is likely suitable for most acutely ill adults with moderate-to-severe AKI. However, variation in case-mix (e.g., cardiorenal syndrome, hepatorenal syndrome, post-cardiac surgery, concomitant organ support with ECLS), and rapid changes in illness acuity and clinical status, and timeliness and availability of essential resources (e.g., vascular access insertion, dialysis equipment, staffing) may influence decision-making. Sound clinical judgement that considers these and other local contextual factors is essential and requires frequent reassessment, especially in rapidly evolving clinical scenarios. Adherence to guidance on RRT initiation can be integrated into best practice advisories and monitored through quality improvement methodology.[743]

Rationale

The decision to start RRT can be complex, given the need to balance perceived benefits and risks, the escalation in resources (e.g., patient transfer, dialysis disposables, human resources), and the importance of shared decision-making that integrates the values and preferences of patients. A fundamental consideration for healthcare professionals when considering whether to start RRT is to ensure clarity in defining the objective(s) and the goal(s) of therapy. Initiation of RRT is appropriate for acutely ill patients with complications attributed to or worsened by AKI, especially if refractory to medical therapy (e.g., hyperkalemia, metabolic acidosis, fluid overload), whose preferences and goals of care are aligned with receipt of RRT. In the absence of urgent indications for RRT, the evidence supports a strategy of deferred timing of RRT initiation over early RRT initiation.

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Practice Point 5.1.2: For children and adults with AKI and high probability of requiring RRT, planning for RRT should be considered before indications are met, including, where applicable and available, transfer to centers with nephrology and RRT services.

Observational studies imply delayed referral to and consultation with specialist nephrology services for selected patients with AKI may portend greater risk for poor outcome, including the risk of life-threatening complications of AKI and need for emergency dialysis.[744-747] There is uncertainty whether this may relate to the availability of specialist nephrology services, including the availability of RRT for acutely ill patients.[708] Nephrologist referral and consultation provide opportunity for long-term continuity of care, follow-up for recognized complications associated with AKI and planning of RRT.[748]

Practice Point 5.1.3: For children and adults with AKI and medically refractory fluid, electrolyte, acid-base, and/or metabolic complications (e.g., uremia), initiate RRT if consistent with patient preferences and goals of care.

There is long-standing general acceptance for the acute initiation of RRT among patients with AKI and medically refractory complications independent of SCr values.[608, 749] RRT in this context is beneficial by effectively treating acutely reversible complications (e.g., hyperkalemia; metabolic acidosis; uremia; fluid overload) and offering opportunity for AKI to resolve. Delay or failure to provide therapy for refractory complications of AKI can portend a high risk for mortality.[124, 711, 730, 750]

Practice Point 5.1.4: Among patients with hepatic encephalopathy (grade ≥2) due to acute or acute-on-chronic liver failure, initiation of continuous RRT (CRRT) to manage hyperammonemia may be considered even when conventional RRT indications are absent.

CRRT can effectively clear ammonia, may reduce cerebral edema, and may be associated with a reduction in mortality among patients with hepatic encephalopathy due to acute or acute-on-chronic liver failure.[751-754] The Work Group concurred with the guidance on the use of CRRT among patients with acute liver failure that were included in the 2023 American Society of Gastroenterology Acute Liver Failure Guidelines.[755]

Practice Point 5.1.5: For critically ill children and adults with AKI, a time-limited trial of RRT can be started if uremic and/or metabolic complications are plausibly confounding neurological evaluation or chances of awakening from coma.

In a secondary analysis of the AKIKI-2 trial, among those people with coma at enrollment, allocation to the more-delayed strategy conveyed lower likelihood of awakening and fewer days awake compared with the delayed strategy.[731] These findings provide

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evidence of the potential risks from complications of persistent severe AKI with longer delays to RRT. A time-limited trial of RRT may be used to facilitate the evaluation and management of potentially modifiable/reversible complications of AKI (Figure 15). Furthermore, a time-limited trial enables an evaluation of the goals of treatment in line with shared-decision making.

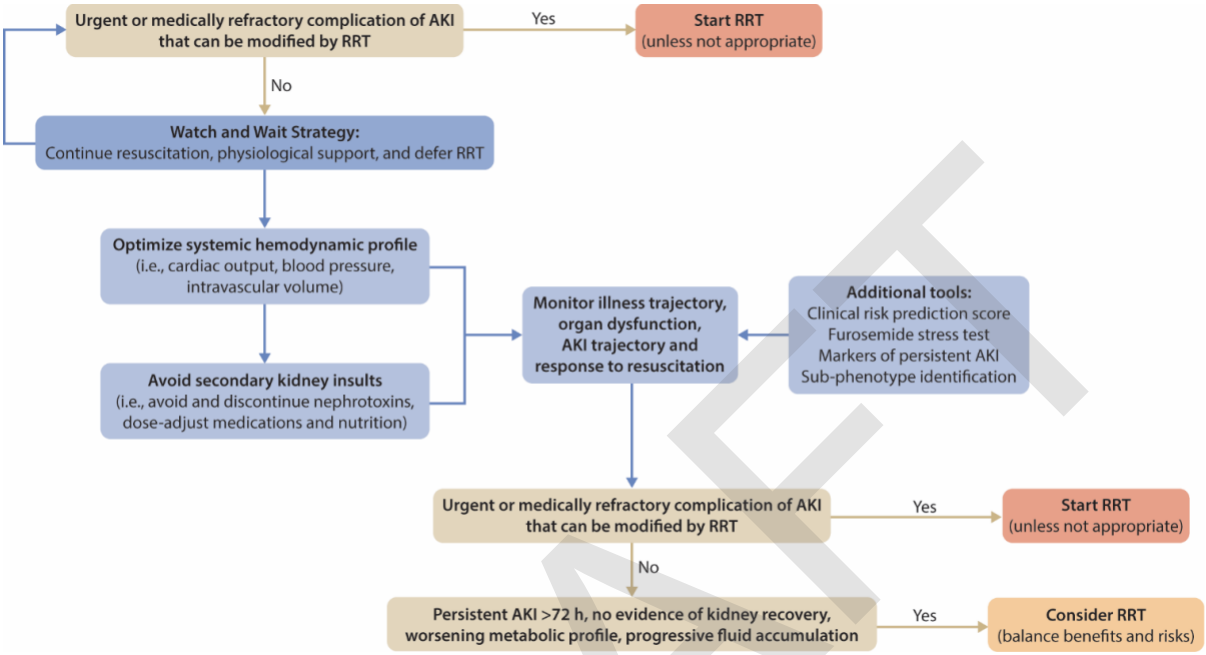
Urgent or medically refractory complication of AKI that can be modified by RRT
Yes
Start RRT (unless not appropriate)
No
Watch and Wait Strategy: Continue resuscitation, physiological support, and defer RRT
Optimize systemic hemodynamic profile (i.e., cardiac output, blood pressure, intravascular volume)
Avoid secondary kidney insults (i.e., avoid and discontinue nephrotoxins, dose-adjust medications and nutrition)
Monitor illness trajectory, organ dysfunction, AKI trajectory and response to resuscitation
Additional tools: Clinical risk prediction score Furosemide stress test Markers of persistent AKI Sub-phenotype identification
Urgent or medically refractory complication of AKI that can be modified by RRT
Yes
Start RRT (unless not appropriate)
No
Persistent AKI >72 h, no evidence of kidney recovery, worsening metabolic profile, progressive fluid accumulation
Yes
Consider RRT (balance benefits and risks)

Figure 15 | Proposed algorithm for initiation RRT in critically ill patients with AKI. AKI, acute kidney injury; RRT, renal replacement therapy. Adapted from Ostermann et al.[756]

Practice Point 5.1.6: For children and adults with AKI, particularly those receiving vasoactive support, identify and treat modifiable factors and mitigators of hemodynamic instability at the commencement of RRT.

Hemodynamic instability during RRT occurs with relative frequency among acute and critically ill children and adults and may portend greater risk of adverse outcomes, including mortality and non-recovery of kidney function.[757-761] Hemodynamic instability commonly occurs upon circuit connection and start of RRT.[757, 759, 762] Patients with greater illness acuity, those receiving vasoactive support, patients exposed to high ultrafiltration rates and neonates and children (where the extracorporeal volume of the circuit is relatively large in proportion to total blood volume) may be more susceptible.[762] Table 44 lists potential RRT related interventions to limit hemodynamic instability during RRT.

5.2. RRT modality

RRT modalities include CRRT, intermittent RRT (IRRT) including the spectrum from conventional intermittent hemodialysis (IHD) to prolonged intermittent RRT (PIRRT), and peritoneal dialysis (PD). All modalities have a role in AKI but vary in their spectrum of benefits and potential complications (Table 42).[763]

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Table 42 | Summary of each RRT modality along with their commonly applied settings, advantages, and disadvantages

Modality	Potential setting in AKI	Advantages	Disadvantages
IHD	• Hemodynamically stable patients • Circumstances necessitating rapid removal of small solutes (e.g., tumor lysis syndrome, drug overdose)	• Rapid removal of small solutes or toxins • Allows for "down time" for diagnostic and therapeutic procedures and interventions • Reduced exposure to anticoagulation • Lower short-term costs than CRRT	• Hemodynamic intolerance and IDH • Dialysis disequilibrium with risk of cerebral edema in cases of rapid removal of osmotically active substances
PIRRT (also referred to as **SLED** or **EDD**)	• Hemodynamically unstable patients	• Slower volume and solute removal • Hemodynamic stability • Allows for "down time" for diagnostic and therapeutic procedures • Reduced exposure to anticoagulation • Use of conventional IHD machines	• Slower clearance of toxins • Lower risk of IDH compared to IHD
CRRT	• Hemodynamically unstable patients • Patients at risk of intracranial hypertension or increased intracranial pressure	• Continuous correction and removal of solutes, metabolites, and toxins with less fluctuations in serum concentrations • Hemodynamic stability • Easy control of fluid balance • Real-time adaptability among critically ill patients with high illness acuity • May reduce the risk of inciting or exacerbating cerebral edema • May be most appropriate for critically ill patients with AKI who are also receiving ECLS, mechanical circulatory support or $ECCO_2R$	• Slower clearance of toxins per hour • Need for specific RRT platform • Need for anticoagulation in most patients • Patient immobilization • Risk of hypothermia • Inadvertent losses of water-soluble nutrients and medications • Increased costs
PD	• Hemodynamically unstable patients • Coagulopathy • Difficult vascular access • Low-resource settings • Preferred RRT modality for selected children with AKI (e.g., complex congenital cardiac surgery)	• Technically simple • Hemodynamic stability • Gradual removal of toxins • Less fluctuations in serum concentrations of osmotically active substances • No need for anticoagulation	• Less control of rate of fluid removal • Lower clearance efficacy compared to IHD or CRRT • Need for peritoneal dialysis catheter • Risk of peritonitis • Risk of pleural effusion in case of diaphragmatic defect

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		• No need for vascular access • Lower resource use	• Hyperglycemia • May negative impact pulmonary compliance and worsen gas-exchange • Requires intact peritoneal cavity and preserved peritoneal membrane • Reduced clearance in conditions associated with reduced bowel motility

CL_{Urea}, ureal clearance; CRRT, continuous renal replacement therapy; ECLS, extracorporeal life support; $ECCO_2R$, extracorporeal CO_2 removal; IHD, intermittent hemodialysis; IDH, intradialytic hypotension; PD, peritoneal dialysis; PIRRT, prolonged intermittent renal replacement therapy; Q_B, blood flow rate; Q_D, dialysis flow rate; Q_R, replacement fluid rate; RRT, renal replacement therapy; SLED, sustained low-efficiency dialysis; UF_{NET}, net ultrafiltration; EDD, extended daily dialysis

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Practice Point 5.2.1: The initial selection of RRT modality in children and adults with AKI, including CRRT, intermittent RRT (IRRT), or acute peritoneal dialysis (PD), should integrate patient characteristics, clinical context, local expertise, and resource availability.

There is a spectrum of RRT modalities used to support acute and critically ill patients with severe AKI who develop indications for RRT. These RRT modalities include extracorporeal support with CRRT and IRRT as well as acute PD. RRT modalities are characterized by differences in application (e.g., access, treatment schedules, dosing) and mechanisms of solute clearance and ultrafiltration (Tables 42 and 43). There are variable practices across clinical settings and geographic regions for the selection of RRT modality for treatment of patients with AKI, due to differences in patient characteristics, clinician expertise and preferences, institutional/organizational factors, and resource availability. Further, patients may transition from one modality to another, for instance from CRRT to IRRT. The ideal timing and clinical circumstances for RRT modality transition are uncertain but are also influenced by patient characteristics and organizational factors.

Recommendation 5.2.1: For critically ill adults with AKI and hemodynamic instability, we suggest using CRRT or acute PD over conventional IRRT *(2C)*.

This recommendation places a high value on the advantages of greater hemodynamic stability reported with continuous forms of RRT, including CRRT and acute PD, over conventional intermittent RRT. The recommendation is focused on the selection of RRT modality for patients with hemodynamic instability because it may exacerbate kidney damage and impair or prolong resolution of AKI. It places a high value on the shorter duration of RRT and ICU stay among patients treated with acute PD over conventional intermittent RRT. This recommendation places a lower value on the greater resource use and costs of CRRT compared with conventional intermittent RRT.

Key information

Balance of benefits and harms

CRRT, IRRT, and PD have specific advantages and potential complications. Compared with IRRT, CRRT and PD enable more gradual ultrafiltration and solute removal and may be particularly advantageous in patients with hemodynamic instability. (Table 43)

A large network meta-analysis found no difference in all-cause mortality, time on RRT, recovery of kidney function, or length of hospital and ICU stay when comparing CRRT with IRRT (Supplementary Table S84).[764] However, studies included in these pooled estimates comprised heterogeneous populations with varying levels of hemodynamic instability (Supplementary Table S82). Moreover, many studies comparing CRRT with IRRT excluded participants with hemodynamic instability because of the perceived risk of harm in randomizing a hemodynamically unstable patient to IRRT. Although the available pooled

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evidence suggested no differences in benefits or harms when comparing CRRT and IHD, the majority of panel members perceived that the theoretical risk of harm with IRRT outweighed the increased incremental cost with CRRT and, therefore, favored CRRT for critically ill patients with hemodynamic instability.

The same network meta-analysis found that compared with IRRT, acute PD reduced the length of time on RRT and ICU stay (with large apparent treatment effects), with no difference in all-cause mortality or recovery of kidney function (Supplementary Table S85).[764] Collectively, this body of evidence suggests important potential benefits with no apparent risk of harm, recognizing that acute PD may not be available in all care settings.

There have been few small, largely single center RCTs[765-770] and systematic reviews[771, 772] that have compared the efficacy and outcomes of acute PD versus extracorporeal RRT, including CRRT and IRRT, for critically ill participants with AKI. Their findings have been largely supported by real-world evidence from observational studies.[773-775] One single center RCT compared acute PD to CRRT in 70 adults with sepsis-associated AKI.[766] While participants allocated to acute PD had worse outcomes, the technique for acute PD was not aligned with current guideline-directed standards (e.g., use of rigid catheters, use of manual exchanges and open drainage, acetate buffered solutions).[776] More recent RCTs have suggested that acute PD can achieve similar and acceptable efficacy and outcomes when compared with extracorporeal RRT; and PD may be associated with less costs and resource use (Supplementary Tables S85 and S86).[765, 767-769, 777]

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Table 43 | Summary of parameters for RRT modalities in adults

	IHD	SLED	SCUF	CVVH	CVVHD	CVVHDF	PD
Q_B (ml/min)	300–500	100–300	100–200	80-200	80-200	80-200	N/A
Mechanism for solute transport	Diffusion*	Diffusion	Convection	Convection	Diffusion	Diffusion & convection	Diffusion
UF_{NET} (ml/kg/h)	0–15	0–8	0–8	0–3	0–3	0–3	variable
Q_D (ml/h)	300–500 ml/min	100–300 ml/min	N/A	N/A	250–2000	250–2000	1–2 l per exchange
Q_R (ml/h)	Variable in HDF	0	N/A	250–4000	0	250–4000	0
CL_{Urea} (ml/min)	200–350	80–90	1–5	25–33	25–33	25–33	15-25
Main access	Central vein	Central vein	Central vein or peripheral vein	Central vein	Central vein	Central vein	Peritoneal cavity
Need for anticoagulation	Usually but not absolutely necessary	Usually but not absolutely necessary	Usually but not absolutely necessary	Usually but not absolutely necessary	Usually but not absolutely necessary	Usually but not absolutely necessary	No
Fluctuations of osmotically active substances	+++	++	+	Less but may occur in case of treatment interruptions	Less but may occur in case of treatment interruptions	Less but may occur in case of treatment interruptions	No
Effect on ICP in patients with acute brain injury	Potentially increased	Potentially increased	Less than with IHD	Less than with IHD	Less than with IHD	Less than with IHD	Usually no change

*Diffusion ± convection when used with hemodiafiltration (HDF). CL_{Urea}, ureal clearance; CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; ICP, intracranial pressure; IHD; intermittent hemodialysis; N/A, not applicable; PD, peritoneal dialysis; Q_B, blood flow rate; Q_D, dialysis flow rate; Q_R, replacement fluid rate; RRT, renal replacement therapy; SCUF, slow continuous ultrafiltration; SLED; sustained low-efficiency dialysis; UF_{NET}, net ultrafiltration

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Certainty of evidence

The certainty of evidence among critically ill adults for selection of initial RRT modality for the treatment of AKI is mostly low to moderate for comparisons of different pairs of modalities. The comparison of CRRT versus IRRT has moderate certainty of evidence,[764] with downgrading mortality and recovery of kidney function due to methodological concerns of the studies and downgrading of time on RRT due to imprecision.

The comparison of IHD and PD has low certainty of evidence,[764, 765] with downgrading of mortality and recovery of kidney function for methodological concerns and sparseness of studies, but upgrading since network meta-analysis was concordant with the findings of the single study; time on RRT was downgraded for a lack of direct comparisons (conclusion was based on network meta-analysis), but with upgrading for a large effect size.

The comparison of CRRT versus PD also had low certainty of evidence,[764] with downgrading of time on RRT for methodological concerns, downgrading of mortality for both methodological concerns and inconsistency across studies, and downgrading of recovery of kidney function for methodological concerns, inconsistency, and imprecision. The certainty of evidence for time on RRT was moderate, but the overall assessment was low certainty of evidence since the certainty for mortality was low.

Values and preferences

This recommendation recognizes the high value and importance that patients and their surrogate decision-makers convey to evidence-based practices that foster resolution of AKI, shorter duration of RRT, and recovery to RRT independence. Resolution of AKI has implications for risk of long-term dialysis dependence, which can contribute to impaired quality-of-life, social disruption, loss of work productivity and independent living, and can be perceived as a burden to patients, including adults who commenced RRT during childhood, caregivers and surrogate decision-makers.[740, 778, 779] Achieving freedom from RRT was perceived as important to patients and associated with greater health-related quality-of-life.[780-782]

Resource use and costs

RRT is generally resource intensive and expensive. Acute care RRT programs, particularly CRRT or RRT in ICU settings, generally demand specialized training and infrastructure, which may not be widely available. Studies have suggested IRRT may be associated with lower costs,[783, 784] due largely to greater disposable costs for CRRT (e.g., circuits, anticoagulation, replacement solutions).[763] However, RRT-specific costs are context-specific and variable and further depend on local procurement and practices.[763] Acute PD is more cost effective compared with continuous or intermittent RRT, particularly when supported by evidence of shorter duration of RRT and ICU length of stay.[785-787] Acute PD is a suitable and important option for selected populations (e.g., children with AKI) and in low-resource settings where CRRT and IRRT may not be available.[771, 776, 788, 789]

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Considerations for implementation

While there is a spectrum of RRT modalities that can be employed to support acutely and critically ill patients with severe AKI with indications for RRT, the real-world implementation of a spectrum of modalities can be challenging. The key factor influencing the availability of selected RRT modalities is equitable access to resources, where low-to middle-resource settings may have limited access to some forms of RRT or, more specifically, to more expensive and resource intensive RRT modalities, or may not have available resources or infrastructure.[788, 790] This may necessitate procedures to organize transfer of acutely ill children or adults, if feasible, to settings where acute RRT services can be provided (Practice Point 5.1.2). The *Saving Young Lives* program has focused on enabling provision of simple acute PD (low cost, no electricity or complex equipment) for acutely ill patients in low-resource settings.[788] This has included education, training, and mentoring of healthcare professionals and serves as a model to broaden access to acute PD globally in low-resource settings.[790] Several practice points for the provision of acute PD have been integrated into the 2020 International Society of Peritoneal Dialysis (ISPD) clinical practice guidelines.[776] Implementation of the *Saving Young Lives* or similar programs should integrate monitoring and data capture aligned with quality improvement methodology.[791]

Rationale

Evidence from RCTs has shown no differences in mortality or RRT dependence with intermittent RRT, including PIRRT), versus CRRT; however, not all comparative trials have been restricted to treatment of patients with hemodynamic instability, and some trials excluded such patients. Evidence from RCTs has shown a shorter duration of RRT with acute PD versus CRRT or IHD, with no differences in mortality or RRT dependence.

Healthcare professionals providing RRT for AKI should appreciate the advantages and limitations of each modality and tailor treatment according to the specific needs of each patient. RRT modality choice should also be informed by the available resources and local expertise.

Practice Point: 5.2.2: CRRT is preferable to conventional IRRT for critically ill children and adults with AKI and acute brain injury or other causes or risks of increased intracranial pressure (ICP) or cerebral edema.

Patients with acute brain injury or cerebral edema may be susceptible to secondary insults that can further compromise cerebral perfusion, exacerbate cerebral edema, and extend existing injury,[792-794] especially in the penumbra surrounding the acute injury where brain tissue may be recoverable. Patients treated with RRT, particularly IRRT, are susceptible to intradialytic hypotension and rapid shifts in serum solute concentration and osmolality.[795] Treatment with IRRT in patients with acute brain injury can alter ICP and provoke new or worsening cerebral edema, the degree of which correlates with the frequency

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of therapy and ultrafiltration.[796] CRRT may be better suited to mitigate rapid fluctuations in solute clearance or fluid removal and reduce the risk of exacerbating cerebral edema. Indeed, acute changes in brain density consistent with new or worsening cerebral edema have been shown to be more likely among patients receiving conventional IHD compared with CRRT.[797] Alternatively, PD may serve as a suitable option for selected adult patients with brain injury, particularly if there are contraindications to systemic anticoagulation. There is limited evidence that has directly compared CRRT and PIRRT in patients with brain injury or acute liver failure and the risk of disequilibrium syndrome and worsening neurological profile. In circumstances where CRRT or acute PD is not feasible or available, the prescription for RRT should be carefully adapted to minimize the risk of intradialytic hypotension and rapid solute clearance associated with shifts in serum osmolality (Table 44).

Practice Point 5.2.3: For children and adults with AKI, particularly those requiring vasoactive support, identify and treat modifiable factors and mitigators of hemodynamic instability during RRT.

Hemodynamic instability during RRT occurs frequently among acute and critically ill children and adults and may portend greater risk of adverse outcomes, including mortality and non-recovery of kidney function.[757-761] Hemodynamic instability commonly occurs upon circuit connection and start of RRT.[757, 759, 762] Patients with greater illness acuity, those receiving vasoactive support, patients exposed to high ultrafiltration rates, and neonates and children (where the extracorporeal volume of the circuit is larger in proportion to total blood volume) may be more susceptible.[762] The use of a passive leg raise (PLR) test in adults and other dynamic hemodynamic measures can further aid in predicting the risk of intradialytic hypotension prior to initiation of IRRT.[798-800]

Greater hemodynamic tolerance to IRRT in acute and critical care settings may be achieved by using strategies to mitigate intradialytic hypotension (Table 44).[761, 801] These strategies can be applied to acute or critically ill patients with AKI upon initiation of IRRT or following transition to IRRT from CRRT. They have largely been adapted from measures to prevent intradialytic hypotension among children and adults with kidney failure receiving maintenance dialysis.[802, 803]

The risk of hypotension can be further addressed by discontinuation of all vasodilators or antihypertensive medications and pre-emptive fluid administration before initiation of RRT. Hyperoncotic albumin solutions may be used in patients with hypoalbuminemia.[804] A further trial is evaluating the role of albumin supplementation to mitigate the risk of intradialytic hypotension among critically ill adults receiving RRT.[805]

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Table 44 | Summary of strategies and interventions to mitigate intradialytic hypotension among adults starting or transitioning to IRRT

Intervention	Description
Patient-specific	
Discontinue vasodilator or antihypertensive medications	Discontinue scheduled anti-hypertensive medications on the day of transition from CRRT or initial IRRT or discontinue any i.v. infusions of vasodilator therapy prior to transition from CRRT or initial IRRT
Supplemental albumin	Give albumin 25% 100 ml i.v. over 15–20 minutes prior to planned initiation of IRRT (for patients with hypoalbuminemia).
Midodrine	Give a single dose of midodrine 2.5–10 mg po 30 minutes prior to or during planned initiation of IRRT.
RRT-specific	
Lower initial blood flow rate (Q_B)	Initiate IRRT at a lower blood flow rate (Q_B ~ 100 ml/min) and increase every 2–5 min by increments of 50–100 ml/min to target blood flow rate.
Lower initial dialysate flow rate (Q_D)	Initiate IRRT at a lower dialysate flow rate (Q_D 300 ml/min) and titrate to target.
Lower temperature dialysate	Initiate IRRT using an initial dialysate temperature <37.0°C and/or <0.5°C below measured body temperature.
Higher dialysis sodium concentration	Initiate IRRT using a higher dialysate [Na] (≥145 mmol/l).
No or low initial ultrafiltration (UF)	Initiate IRRT with zero ultrafiltration and titrate to target.

CRRT, continuous renal replacement therapy; IRRT, intermittent renal replacement therapy; i.v., intravenous; Na, sodium; PIRRT, prolonged intermittent renal replacement therapy; po, oral; RRT, renal replacement therapy

Practice Point 5.2.4: Prolonged IRRT (PIRRT) is an acceptable alternative to CRRT as the initial RRT modality for hemodynamically unstable, critically ill adults with AKI.

PIRRT refers to intermittently applied RRT for periods longer than conventional IHD (e.g., 6–12 hours). PIRRT, often referred to as SLED or extended daily dialysis (EDD), aims to realize the theoretical benefits of both CRRT and conventional IHD while mitigating risks, particularly intradialytic hypotension (Table 44).[806-808]

Practice Point 5.2.5: Transition from CRRT to IRRT can be considered when children and adults who have not recovered from AKI are physiologically and metabolically able to tolerate IRRT and the risks of intracranial hypertension or cerebral edema, if applicable, are resolved.

Approaches to transition of patients between RRT modalities during phases of organ function recovery, particularly CRRT to IHD, have undergone limited evaluation in critically ill patients with AKI .[809-811] A period of receipt of IHD is common following CRRT, occurring in 36%–50% of instances, usually after hemodynamic stability has been achieved and care is focused on rehabilitation and mobilization.[809, 810] Several patient factors predict intolerance to transition to IRRT and IHD, including hypoalbuminemia, ongoing fluid

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accumulation, oliguria, use of vasopressors, and use of mechanical ventilation, which can guide decision-making about the appropriate timing.[761]

5.3. RRT dose-intensity

Recommendation 5.3.1: We recommend delivering an effluent volume of 20-25 ml/kg/h over higher volumes for solute clearance in adults receiving CRRT, or a Kt/V of 3.9 per week over higher urea clearance in adults receiving IRRT or PIRRT for AKI (*1B*).

This recommendation places a high value on minimizing harms and unnecessary resource use and costs associated with augmented (higher) RRT dose-intensity to achieve greater small solute clearance. While earlier RCTs implied there may be a survival benefit with augmented RRT dose-intensity in critical illness, more recent RCTs, including 2 large multicenter RCTs and several systematic reviews have found no improvement in outcomes with augmented (higher) RRT dose-intensity of solute clearance over standard dose-intensity in acute and critically ill participants with AKI. Current evidence suggests that standard dose-intensity may contribute to fewer days of RRT compared with receipt of higher RRT dose-intensity, with no differences in mortality or long-term RRT dependence.

Key information

Balance of benefits and harms

This recommendation has not changed since the KDIGO 2012 Guideline.[608] The current evidence demonstrates that augmented (higher) RRT dose-intensity (e.g., CRRT dose-intensity ≥35 ml/kg/h; daily sessions of SLED/IRRT targeting a Kt/V ≥1.2) does not improve outcomes compared with a lower RRT dose-intensity (e.g., CRRT dose-intensity 20–25 ml/kg/h or thrice weekly of SLED/IRRT targeting a Kt/V ≥1.2), in terms of improved survival or greater likelihood of resolution of AKI and RRT independence. Moreover, augmented RRT dose-intensity may contribute to RRT-associated morbidity. Secondary analyses of RCTs have suggested that augmented RRT dose-intensity may propagate oliguria and extend total dialysis treatment time.[812, 813] Augmented RRT dose-intensity may increase the risk of cardiac arrhythmias, contribute to hypophosphatemia and electrolyte losses,[814, 815] and increase the risk of delayed weaning from invasive mechanical ventilation,[815, 816] or risk of reintubation.[814, 816] These findings suggest there is no incremental benefit to augmented RRT dose-intensity beyond the lower standards used in prior RCTs.[812, 815, 817-820]

Several small retrospective studies from Japan have evaluated the association of lower-than-standard CRRT dose-intensity (CRRT dose-intensity 10–20 ml/kg/h) with metabolic control and outcomes.[821-825] These studies have suggested that lower CRRT dose-intensity can be tolerated and achieve comparable efficacy for electrolyte, acid-base, and metabolic control as the current standard; however, the comparative effectiveness of this lower dose-intensity on clinical outcomes has not been proven in RCTs. In select jurisdictions (e.g., Japan), lower RRT dose-intensity is routinely delivered and

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recommended.[821-825] There are ongoing RCTs evaluating whether lower RRT dose-intensity can impact survival and resolution of AKI and dialysis dependence.[826-828]

Certainty of evidence

Based on evidence current for the KDIGO 2012 Guideline,[608] there was moderate certainty of evidence overall, with moderate certainty regarding mortality, which was downgraded for inconsistency across studies, and high certainty of evidence for RRT dependence (duration of RRT or to kidney function recovery)

Values and preferences

This recommendation recognizes the importance of adopting the standard RRT dose-intensity to minimize harm, reduce practice variation, and mitigate adverse effects that may be incrementally associated with augmented RRT dose-intensity. The current standard RRT dose-intensity may contribute to fewer days of RRT compared with receipt of higher RRT dose-intensity, which is perceived as important to patients and associated with greater health-related quality-of-life.[780-782]

Resource use and costs

Augmented RRT dose-intensity is a low-value practice that is currently not supported by evidence. Moreover, the routine use of excess RRT dose-intensity may contribute to the risk of adverse events, greater use of RRT disposables, higher bedside workload, increased healthcare costs, and a higher burden on the environment. As such, the current standard RRT dose-intensity will use less resources and translate into relatively lower costs.

Considerations for implementation

Abundant evidence suggests RRT dose-intensity is poorly monitored and susceptible to wide practice variation.[713, 829, 830] The real-world implementation of RRT dose-intensity standards should align and be integrated with quality improvement initiatives aimed at establishing and sustaining high-quality acute RRT programs.[743, 791, 831-833] RRT dose-intensity is an important quality and performance indicator of acute RRT adequacy.[834] In a single centre quality improvement initiative, Griffin *et al*. aimed to standardize CRRT dose-intensity and reduce practice variation.[832] The primary outcome was percentage of weekly CRRT delivered that was concordant with the guideline-directed standard (20–25 ml/kg/h). The baseline concordance was 33%; however, following implementation, compliance increased to 66% over a near two-year period with a substantial reduction in week-to-week variation.

Rationale

RRT dose-intensity is focused on small solute clearance and the correction of complications related to derangements in electrolytes, acid-base balance, or metabolic waste products. The optimal RRT dose-intensity for acutely ill patients with AKI across the spectrum of illness is unknown. Further, the methods used for RRT dose quantification in

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patients with AKI have several limitations and have not been fully validated in this population.

RCTs to date have generally compared augmented (higher) and standard (lower) RRT dose-intensity regimens.[815, 819, 835-837] While earlier RCTs implied there may be a survival benefit with augmented RRT dose-intensity in critical illness,[836, 837] subsequent RCTs, including 2 large multicenter RCTs and several systematic reviews have found no improvement in outcomes with augmented RRT dose-intensity in acute and critically ill participants with AKI.[812, 815, 817, 818, 820, 835] While most RCTs have predominantly included participants receiving CRRT, 3 RCTs had significant proportions receiving IRRT or focused solely on IRRT.[820, 838-840]

In all these RCTs that focused on RRT dose-intensity, dosing regimens (augmented vs. standard) have generally been fixed and not adapted or modified after initial stabilization of acid-base, electrolyte, or metabolic derangements. Whether a strategy of personalized RRT dose-intensity modification can favorably impact clinical outcomes is unknown.

Practice Point 5.3.1: An initial CRRT dose-intensity for adults with high body mass index (BMI; e.g., ≥30 kg/m^2) based on ideal or adjusted body weight, rather than actual body weight, can be used to avoid delivery of excess CRRT dose-intensity.

To date, the preferred reference "weight" (i.e., actual, adjusted, ideal) to calculate the prescribed RRT dose-intensity across the spectrum of BMI encountered in clinical practice is uncertain. In the Veterans Affairs (VA)/National Institute of Health (NIH) Acute Renal Failure Trial Network (ATN) trial, premorbid obesity was considered in the CRRT dose-intensity calculation.[820] In non-obese participants, the CRRT dose-intensity prescription was "based on the weight before the onset of acute illness"; however, in obese participants, defined as a weight exceeding 30% ideal body weight, the prescription was adjusted, calculated as ideal body weight plus 25% of the difference between ideal and actual weight before the onset of acute illness. In addition, participants weighing >120 kg were excluded.[820] In the Randomized Evaluation of Normal versus Augmented Level (RENAL) trial, the prescribed CRRT dose-intensity was "based on the patient's body weight at the time of randomization" and participants weighing <60 kg or >100 kg were excluded.[815]

A recent retrospective cohort study of 1033 critically ill patients receiving CRRT evaluated the association between measures of body weight (i.e., actual, adjusted, ideal), CRRT dose-intensity, and outcome.[841] Ideal body weight was calculated using the Devine formula (males: 50 kg + [2.3 kg × each inch over 60 inches]; females: 45.5 kg + [2.3 kg × each inch over 60 inches]).[842] Adjusted body weight was calculated as ([actual body weight–ideal body weight] × 0.4) + ideal body weight.[841] The cohort was stratified by BMI ≥30 kg/m^2 and CRRT dose-intensity was further indexed by actual body weight, adjusted body weight and ideal body weight. The mean (standard deviation [SD]) CRRT dose-intensity

varied significantly across measures of body weight, particularly among patients with BMI ≥30 kg/m^2 (Table 45).

Table 45 | Summary of varying CRRT dose-intensity stratified by BMI and body weight calculation

	CRRT dose-intensity (ml/kg/h)	
	BMI <30 kg/m^2	**BMI ≥30 kg/m^2**
Actual body weight, (mean [SD])	30 (9)	27 (7)
Ideal body weight, (mean [SD])	37 (10)	48 (14)
Adjusted body weight, (mean [SD])	33 (9)	36 (9)

p<0.001 for each comparison. BMI, body mass index; CRRT, continuous renal replacement therapy; SD, standard deviation. Adapted from Peters et al[841]

There was suggestion of effect modification of CRRT dose-intensity for mortality by measures of body weight. Among obese patients, higher CRRT dose-intensity calculated by actual and adjusted body weight was associated with greater mortality; however, there was no association with mortality when ideal body weight was used.[843]

These observations have implications for CRRT dose-intensity prescribing among patients who are obese (BMI ≥30 kg/m^2) and/or have actual body weights exceeding 100–120 kg, who were not represented in landmark trials guiding CRRT dose-intensity.[815, 820] For patients with a high BMI, the calculation of the initial prescribed CRRT dose-intensity based on ideal or adjusted body weight rather than actual body weight may avoid delivery of excess CRRT dose-intensity.[841] The CRRT dose-intensity can thereafter be adjusted for adequacy and correction of electrolyte, acid-base and metabolic (e.g., nitrogenous waste) derangements.

Recommendation 5.3.2: We recommend not prescribing high-volume hemofiltration (HVHF) compared with standard CRRT dose-intensity for critically ill adults with AKI in the setting of sepsis or septic shock (*1B*).

This recommendation places high value on avoiding potential harms and costs in the absence of any evidence of benefit with HVHF. Compared with standard CRRT dose-intensity (total effluent fluid volume 20-25 ml/kg/h), HVHF (total effluent fluid volume ≥45 ml/kg/h) does not improve mortality or kidney recovery, or reduce serious adverse events and may increase the risk of metabolic complications and excessive clearance of nutrients and medications.

Key information

Balance of benefits and harms

Pooled evidence from systematic reviews of RCTs has found no evidence for benefit of HVHF compared with standard CRRT dose-intensity for any clinical outcomes, including mortality and kidney recovery.[844, 845] A small RCT of 20 critically ill participants with septic shock randomly allocated to CRRT at 35 ml/kg/h or 65 ml/kg/h found no significant difference in any clinical outcome measured.[846] In a single center RCT in China, 280 critically ill participants with sepsis and AKI were randomly allocated to receive CRRT at 50

ml/kg/h (HVHF) or 85 ml/kg/h (extra HVHF).[847] There was no evidence of differences in survival or resolution of AKI between the 2 HVHF groups, respectively. In the multicenter hIgh VOlume in Intensive Care (IVOIRE) trial, 140 critically ill participants with septic shock and AKI were randomly allocated to 96 hours of CRRT at 70 ml/kg/h (HVHF) or 35 ml/kg/h.[848] The trial was terminated prematurely for futility with no evidence for differences in early improvement in organ function or organ support or in the primary outcome of 28-day mortality. In the Hemofiltration to Rescue Severe Shock following Cardiac Surgery (HEROICS) trial, focused on 224 post-cardiac surgery participants with vasoplegic shock, of whom >40% were receiving ECLS, randomization to a strategy of 48 hours of CRRT at 80 ml/kg/h (HVHF) followed by standard CRRT compared with standard of care (where only 57% received CRRT) did not improve time to shock resolution, AKI resolution, or survival.[718]

Systematic review of RCTs has found no evidence for benefit of HVHF compared with standard CRRT dose-intensity for any clinical outcomes, including mortality and kidney recovery (Supplementary Table S87).[814, 817, 849-852] Twelve trials conducted in critically ill adults consistently found no significant difference between intensive and less intensive (standard) CRRT dose for 30-day mortality (RR: 0.95; 95% CI: 0.85–1.05), with similar findings among trials that defined intensive CRRT as either ≥40 ml/kg/h (RR: 0.98; 95% CI: 0.86 –1.11) or ≥45 ml/kg/h (RR: 0.93; 95% CI: 0.83–1.06). Smaller numbers of trials also found no significant differences in likelihood of 30-day complete resolution, or hospital or ICU length of stay. A single trial reported no significant differences in serious adverse events.[851]

In addition to lack of benefit, there is concern that exposure to HVHF may be associated with risk of adverse events, including the undue clearance of electrolytes, nutrients, and medications (e.g., antimicrobials). In the HEROICS trial, more participants in the HVHF arm experienced hypophosphatemia, metabolic alkalosis, and thrombocytopenia.[718] Moreover, those allocated to the HVFH group had longer median durations of RRT (5 days vs. 2 days, $P<0.0001$).

Certainty of evidence

There was moderate certainty of evidence for lack of efficacy of HVFH versus standard dose-intensity CRRT in adults. The certainty of evidence was downgraded for mortality and complete resolution for some methodological concerns across studies. The certainty of evidence for serious adverse events was very low due to methodological concerns and sparseness of evidence. Sub analyses of studies comparing either HVHF with ≥45 or ≥40 ml/kg/h were further downgraded for imprecision.

Values and preferences

This recommendation places high value on avoiding a low-value practice, both from the perspective of the patient and the healthcare system, where HVHF has not been proven to

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improve clinical outcomes, may be associated with uncertain risk, and likely contributes to greater health resource use and associated costs.

Resource use and costs

The use of HVHF can plausibly increase bedside workload for nursing and other personnel due to the need for more frequent changes to replacement/dialysate solution bags and added requirements for electrolyte supplementation. This translates into greater costs for disposables, medications, and nursing time.

Considerations for implementation

The practice of prescribing higher than guideline-directed CRRT dose-intensity remains common despite no evidence of improvement in outcomes.[713, 829, 830] There is no role for HVHF in routine clinical practice beyond enrollment in a RCT in critically ill patients with shock states.

Rationale

Several RCTs have explored whether HVHF can more rapidly restore organ dysfunction (i.e., hemodynamic stability) and improve outcomes.[718, 846-848, 853, 854] These trials have largely focused on critically ill patients with sepsis or following cardiac surgery. Based on currently available evidence, there is no rationale for treating patients with HVHF outside a clinical trial.

Practice Point 5.3.2: The adequacy of the RRT dose-intensity to correct for electrolyte, acid-base, and metabolic (e.g., nitrogenous waste) derangements should be reviewed daily for CRRT and prior to starting each RRT session for IRRT and the prescription adjusted when needed.

Review of a patient's clinical, physiological, and laboratory values, including checking for resolution of AKI, is important before prescribing RRT. For patients who are receiving CRRT or PD, these variables can be reviewed daily (or more often).[791, 834] For patients receiving IRRT, these variables can be reviewed prior to each scheduled session.

CRRT dose-intensity, a surrogate for small solute clearance, is represented by total effluent volume (i.e., replacement fluid + dialysate fluid + ultrafiltration) normalized for patient weight and treatment time (Table 46).[855]

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Table 46 | Summary of calculation of CRRT dose-intensity across CRRT modes[855]

CRRT mode	Calculation of total effluent volume rate (ml/h)
CVVH	Sum of total replacement fluid rate (ml/h) + fluid removal rate (ml/h)
CVVHD	Sum of dialysate fluid rate (ml/h) + fluid removal rate (ml/h)
CVVHDF	Sum of replacement fluid rate (ml/h) + dialysate fluid rate (ml/h) + fluid removal rate (ml/h)

Total replacement fluid rate = prefilter replacement fluid rate (ml/h) + postfilter replacement fluid rate. Calculation of the dilution due to prefilter replacement fluid = plasma flow rate (ml/h)/(plasma flow rate [ml/h] + prefilter replacement fluid rate [ml/h]). CRRT, continuous renal replacement therapy; CVVH, continuous venovenous hemofiltration, CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration.

Evidence from clinical trials, observational studies, and surveys of practice have found that the delivered RRT dose-intensity for solute clearance is often lower than the prescribed dose.[815, 839, 856-861] This discrepancy can be attributed to reduction in hemofilter efficiency and function over time, which may correlate with increases in transmembrane pressure indicating filter clogging. Other reasons include therapy disruptions from alarms that suspend the blood flow pump (e.g., catheter dysfunction or high-pressure alarms), scheduled changes to replacement solutions, hemofilter/circuit loss due to clotting or scheduled change, and other unplanned interruptions (e.g., downtime for diagnostic imaging; transfer to operating theatre, etc.). For these reasons, the KDIGO 2012 Guideline recommended that a higher effluent volume should be prescribed to deliver the recommended effluent volume.[608]

In IRRT, Kt/V is a measure used to quantify dialysis adequacy, defined as the blood clearance of urea (K), multiplied by the treatment time (t), divided by the volume of distribution for urea in the body (V). The urea reduction ratio (URR) has also been used as a measure of adequacy of an IRRT session, defined as the percentage difference between the blood urea concentration before and after a dialysis session. Early clinical studies in patients receiving maintenance dialysis found a dose-gradient relationship with mortality, whereby increasing dose-intensity increased survival to an upper boundary of a Kt/V 1.3 and URR 70%, beyond which no further improvement was evident.[862, 863] Clinical practice guidelines for maintenance hemodialysis recommend delivering a Kt/V 1.2 thrice per week.[864] In AKI, the recommended dose-intensity for IHD is extrapolated from these recommendations but has undergone limited validation.[862]

Discrepancy between prescribed and delivered dose-intensity has also been shown in patients receiving IRRT. The lower delivered than prescribed dose-intensity is associated with use of temporary vascular catheters necessitating reduced blood flow rates, and no anticoagulation use contributing to filter clotting.

Recent advances in IRRT platforms have enabled online clearance monitoring.[865] Online clearance monitoring uses conductivity measurements of the dialysate to estimate Kt/V, by measuring the difference in conductivity between the dialysate entering and exiting

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the dialyzer, which is related to the concentration of sodium ions (as a surrogate for urea). Although online clearance monitoring can provide a non-invasive, real-time method for assessing IRRT adequacy, the Kt/V estimated by this method has been shown to underestimate the delivered Kt/V.[865, 866]

Practice Point 5.3.3: When using acute PD for adults with AKI, deliver a weekly Kt/V of 2.2 (18-24 l PD fluid/day) over higher doses.

The Work Group concurs with the guidance on prescribing and achieving adequate clearance in acute PD that were specifically addressed in the 2020 updated International Society for Peritoneal Dialysis (ISPD) guidelines for PD in AKI (Adults).[776] Acute PD delivered at a dose-intensity targeted to achieve a weekly Kt/V of 2.2 (18-24 l PD fluid per day) can achieve comparable metabolic control (i.e., urea, creatinine, bicarbonate, potassium, sodium concentrations), duration of therapy, and mortality to that of extracorporeal RRT and higher intensity PD.

In a single center RCT from 2008, Gabriel *et al*. compared high-volume PD (36-44 l PD fluid/24 hours–delivered Kt/V 3.6) with daily IHD (Kt/V 4.7) in 120 critically ill participants with AKI.[768] Metabolic control (i.e., urea, creatinine, bicarbonate, potassium, sodium, glucose) and mortality [58% vs. 53%, *P*=0.71] was similar; however, participants treated with high-volume PD had shorter duration of therapy (5.5 days vs. 7.5 days, *P*=0.02) and earlier resolution of AKI (7.2 days vs. 10.6 days, *P*=0.04) compared with daily IHD. An RCT comparing lower dose-intensity PD (18-24 l PD fluid/day during the first 2 days; delivered weekly Kt/V of 2.11) with IHD thrice per week (delivered weekly Kt/V of 2.81) found no difference in outcome. A multicenter RCT compared acute lower dose-intensity PD (18–24 l/day) with IRRT among participants with AKI and found no significant differences in 28-day mortality or RRT-free survival between groups.[765]

Several studies have also applied lower-volume PD with acceptable results.[867-870] In a single center RCT, Ponce *et al*. randomly allocated 61 critically ill participants to high (Kt/V 0.8 per session) versus low dose-intensity PD (Kt/V 0.5 per session).[869] Metabolic control, duration of therapy, and mortality were similar, implying a lower Kt/V target could be applied. This translates into lower fluid volumes use, fewer resources, and lower costs. In another single center RCT, 75 acutely ill participants with AKI were allocated either to lower dose-intensity PD (<20 l PD fluid/day; delivered Kt/V 2.26) or higher dose-intensity PD (>30 l PD fluid/day; delivered Kt/V 3.30) using a single-bag open system (1.5 l PD fluid) for the first 2 days.[870] There were no significant differences in metabolic control, hospital mortality (72% vs. 63%, *P*=0.8), or resolution of AKI; however, those allocated to higher dose-intensity PD had a trend towards more peritonitis (15.3% vs. 8.3%, *P*=0.34). Whether acute PD is as effective as standard extracorporeal RRT dose-intensity among patients with marked hypercatabolic or shock states with splanchnic hypoperfusion is unknown.

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Delivering a standard dose-intensity of acute PD is a feasible, safe, and comparably effective form of acute RRT that can extend treatment options for patients with AKI in low-resource settings or among selected populations where conventional extracorporeal RRT is less feasible or practically challenging. If acute PD is the only option available to patients with severe AKI confronted with severe electrolyte, acid-base, metabolic, and fluids complications, it can be lifesaving.[788, 790, 871-873] Using standard dose-intensity acute PD also necessitates fewer resources and can realize cost savings when compared to extracorporeal RRT and higher dose-intensity PD that requires greater volumes of PD solutions and more intensive nursing support for delivery.[777, 867] In general, acute PD requires less infrastructure (i.e., water; electricity), simpler training for healthcare personnel, and can be performed using less resources and costs.[777, 867] This makes acute PD using standard dose-intensity an appealing choice for implementation in low-resource settings, where it has been proven feasible and effective through initiatives such as the *Saving Young Lives* program.[788, 790, 871-873]

Practice Point 5.3.4: In adults with AKI, the initial PD prescription, including duration of cycle time and glucose concentration of PD fluid, may need to be modified to rapidly correct acid-base, electrolyte, metabolic, or fluid complications in adults with AKI.

The Work Group concurred with the guidance regarding the initial prescription and delivery of acute PD among adults with AKI that was detailed in the 2020 updated ISPD guidelines for PD in AKI (Adults) (Figure 16).[776] In adults with AKI, the initial PD prescription, including, duration of cycle time and glucose concentration of PD fluid, may need to be modified to rapidly correct acid-base, electrolyte, metabolic, or fluid complications in adults with AKI, particularly in critically ill or hypermetabolic patients. To achieve target fluid removal during the initial prescription, variable glucose-containing PD fluid and/or shorter cycle times may be used. The cycle time can then be extended and modified based on patient and clinical circumstances (4-6 hours).

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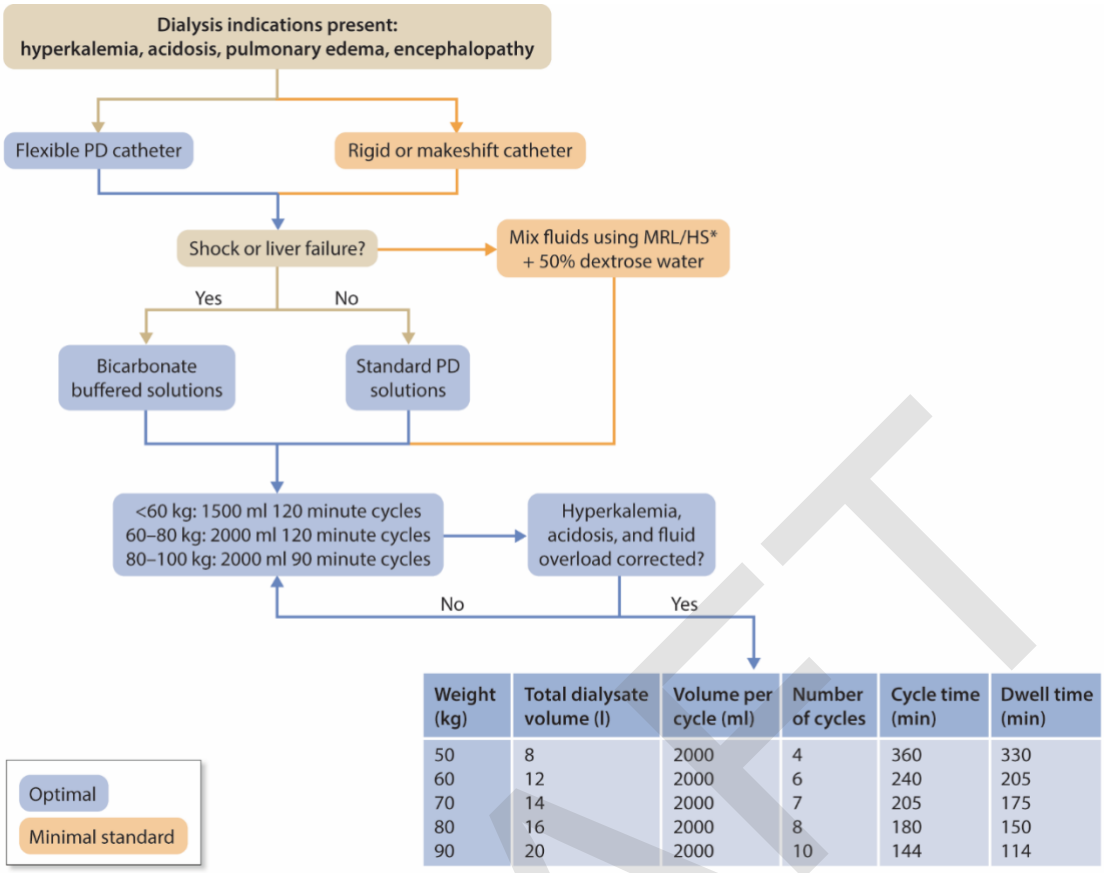

Weight (kg)	Total dialysate volume (l)	Volume per cycle (ml)	Number of cycles	Cycle time (min)	Dwell time (min)
50	8	2000	4	360	330
60	12	2000	6	240	205
70	14	2000	7	205	175
80	16	2000	8	180	150
90	20	2000	10	144	114

Figure 16 | Suggested algorithm for use of acute PD among adult patients with AKI. AKI, acute kidney injury; HS, Hartmanns solution; MRL, modified Ringers lactate; PD, peritoneal dialysis. Reproduced from Cullis et al[776].

Automated PD using 25 l/day with 70% tidal volume in adults with AKI is approximately equivalent to a CRRT effluent volume of 23–24 ml/kg/h. This estimate of dose equivalence was derived from a single RCT including 125 critically ill adults with AKI in whom tidal acute PD (25 l PD fluid/day; fill volume 2.0 l; tidal volume 70%) was compared with continuous venovenous hemodiafiltration (CVVHDF; prescribed total effluent fluid rate 30 ml/kg/h).[767] Survival (69.8% vs. 46.8%, P<0.01), AKI resolution (60.3% vs. 35.5%, P<0.01) and infectious complications (9.5% vs. 17.7%, P<0.01) were significantly better in those allocated to acute tidal automated PD compared with CVVHDF. The delivered CVVHDF dose-intensity was 23.5 ml/kg/h.[608, 776]

5.4 Catheters for RRT

Practice Point 5.4.1: Vascular access for RRT, including type, size, length, and site of catheter placement, should consider feasibility and weigh the risks of catheter colonization/infection or bleeding with the desire to maintain catheter/circuit patency in children and adults.

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The selection of dialysis catheters for acute RRT in critically ill children and adults should be guided by a balance between the feasibility of insertion, the risk of complications (e.g., catheter colonization, infection, and bleeding), and the need to maintain circuit patency and achieve adequate blood flow. In acute settings, nontunneled, uncuffed catheters are recommended due to their ease of insertion, immediate usability, and suitability for short-term use. This is particularly relevant in ICU settings, where rapid initiation of therapy is often required. Cuffed tunneled catheters are not typically necessary unless prolonged RRT access is anticipated or a transition to chronic maintenance dialysis is planned for patients with AKI superimposed on advanced CKD.[608, 820]

The right internal jugular vein is preferred for catheter placement in both children and adults.[874] This site provides the most direct route to the superior vena cava and right atrium, reducing the risk of catheter malfunction, kinking, and malposition.[875] Additionally, the right internal jugular vein is associated with lower rates of catheter-related bloodstream infection and thrombosis compared to other sites.[876]

The subclavian vein should be avoided, particularly in adults, due to the high risk of central venous stenosis, which can compromise future vascular access options. This is critical for patients who may later require longer-term or chronic maintenance dialysis.[820, 877] In children, central venous stenosis also occurs after central line placement, but reported rates are generally lower and are influenced by factors such as the number and type of catheters, device size, and prior central venous access exposure.[878-880] Femoral access may be considered when internal jugular access is not feasible, although it carries a higher risk of infection, particularly in obese or immobilized patients.[877, 881]

For adults, catheters of at least 12 French (F) in size are recommended to allow sufficient blood flow rates (ideally ≥200–250 ml/min) and reduce the risk of circuit clotting or inadequate RRT delivery.[608, 820] Adequate blood flow is essential for effective solute clearance, ultrafiltration, and anticoagulation management. Catheter length should be tailored based on insertion site to ensure the catheter tip reaches the cavoatrial junction for right or left internal jugular approach and inferior vena cava for femoral access. Peres *et al.* proposed formulas based on patient height and insertion site to estimate optimal catheter length, which were later validated by Czepizak *et al.* with 90%–97% accuracy.[882, 883] Optimal lengths include 15 cm for right internal jugular placement, 20 cm for left internal jugular, and 20–25 cm for femoral placement (Table 47). Correct tip placement minimizes recirculation, reduces the risk of mechanical dysfunction, and ensures efficient RRT delivery.

There are no universal French size cutoff values for pediatric dialysis catheters. Size selection should be proportional to patient weight and vessel diameter to ensure adequate blood flow while minimizing the risk of vascular injury (Table 48).[884, 885]

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Confirming proper catheter tip position is generally recommended, ideally at the cavoatrial junction for internal jugular catheters or within the inferior vena cava for femoral access. While chest roentgenography remains the most used method, emerging techniques such as ultrasound-guided tip visualization or intracardiac electrocardiogram-guided can enhance tip confirmation in select settings.[886-889]

Table 47 | Peres' formulas for determining catheter length in adults[882, 883]

Site	Formula	Accuracy
Right internal jugular	Height/10 cm	90%
Left internal jugular	Height/10+4 cm	94%
Right subclavian	Height/10-2 cm	96%
Left subclavian	Height/10+2 cm	97%

Table 48 | Common pediatric dialysis catheter sizes based on child weight[875, 890, 891]

Patient weight (kg)	Catheter size (French)	Notes
<5	4.5–6	Use the smallest size to fit the vessel; single lumen dual access can be used
5–15	7–8	Infants/small children
15–30	8–10	Children
>30	10–12	Adolescents

Practice Point 5.4.2: Adoption of standardized care bundles for dialysis catheter insertion and maintenance can reduce the risk of complications.

Uncuffed non-tunneled dialysis catheters are essential for timely initiation of acute RRT, but they carry a risk of complications and dysfunction that may impair RRT effectiveness and negatively impact patient outcomes.[875] These complications are broadly classified into early and late events and are often preventable with use of standardized care bundles for catheter insertion and maintenance.[892, 893] Early catheter dysfunction typically occurs within the first hours to days following insertion and is most often due to technical factors, such as suboptimal catheter placement, incorrect positioning of the catheter tip, or mechanical kinking.[875, 894] Misplacement may lead to inadequate blood flow, significant recirculation, or failure to deliver adequate dialysis dose-intensity. The use of ultrasound and real-time imaging guidance, along with strict adherence to insertion protocols, can substantially reduce these risks.[886-889]

Late catheter dysfunction commonly results from intrinsic or extrinsic obstruction, including thrombus formation at the catheter tip or within the vessel, and fibrin or biofilm sheath formation. These obstructions impair circuit flow and often necessitate catheter exchange.[875] Catheter-related bloodstream infections represent a major late complication, contributing to increased morbidity, prolonged hospitalization, and mortality.[895]

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The KDOQI 2019 Clinical Practice Guidelines for Vascular Access strongly advocate for the implementation of care bundles, which are structured sets of evidence-based practices that, when performed collectively and reliably, have been shown to improve outcomes.[875] These bundles typically include use of maximal sterile barriers during insertion, chlorhexidine for skin antisepsis, daily catheter site assessment, proper hub disinfection, securement techniques, and timely removal of unnecessary catheters. Implementation of such standardized care bundles has been demonstrated to reduce catheter-related infections, improve catheter function, and extend catheter survival (Table 49).[895, 896]

In addition to care bundles, catheter lock solutions are being increasingly explored as adjunctive measures to reduce catheter-related infections. A recent meta-analysis found that citrate locks showed a trend toward lower infection and complication rates compared to heparin or saline.[897, 898] Taurolidine-heparin lock solution was associated with a 71% risk reduction in catheter-related bloodstream infections compared to heparin alone, although most current evidence is extrapolated from evidence from studies conducted in patients with tunneled or long-term catheter placement for maintenance dialysis.[899, 900]

Table 49 | Summary of the elements in the standard care bundle for non-cuffed dialysis catheters[875]

Component	Recommendation
Catheter site selection	Prefer right internal jugular vein for insertion; avoid subclavian vein to prevent central vein stenosis.
Ultrasound guidance	Use real-time point-of-care ultrasound (POCUS) to guide catheter insertion and confirm placement.
Aseptic technique	Strict maximum sterile barrier precautions during insertion.
Catheter securement	Use sutures or securement device to minimize movement and reduce infection risk.
Dressing protocol	Apply chlorhexidine-impregnated dressing and change per institutional policy or when soiled/loose.
Exit site care	Perform regular exit site cleaning with antiseptic solution.
Catheter locking	Use anticoagulant lock (e.g., heparin, citrate) or antimicrobial lock if infection risk is high.
Documentation & monitoring	Document insertion details and monitor daily for signs of infection or dysfunction.
Timely removal	Remove catheter as soon as no longer needed or if signs of infection/dysfunction.
Education & training	Ensure staff are trained in insertion, care, and early recognition of complications.

Practice Point 5.4.3: Use of existing arteriovenous fistulas/grafts may be suitable for IRRT in children and adults to avoid new dialysis catheter placement.

Practice Point 5.4.4: It is preferable to avoid using existing arteriovenous (AV) fistulas/grafts for CRRT in children or adults, due to concern for needle dislodgement or arteriovenous fistulae/graft damage with prolonged cannulation.

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In the acute care setting, vascular access choice is a vital component of safe and effective RRT. While existing AV fistulas or AV grafts are preferred for maintenance hemodialysis due to their durability and lower risk of infection, their role in short term RRT, particularly CRRT, is more nuanced. For IRRT in hemodynamically stable children and adults, the use of a well-functioning, mature AV fistula/grafts may be appropriate. This approach avoids the insertion of a temporary dialysis catheter, thereby reducing the risk of catheter-associated complications such as infection, bleeding, thrombosis, and venous stenosis.[875, 901] This is especially relevant in patients who are already established on maintenance hemodialysis or who have a functioning vascular access created in anticipation of maintenance dialysis initiation.

In contrast, the routine use of AV fistula/grafts for CRRT is generally not recommended due to several concerns. The prolonged cannulation necessary for CRRT poses a significant risk of needle dislodgement, particularly in critically ill, sedated, or agitated patients who may move unpredictably. The mechanical stress from 24-hour continuous blood flow through large-bore dialysis needles may contribute to vessel wall trauma or damage to the anastomosis site, especially in newly created or maturing accesses. Unnikrishnan *et al.* showed that venous needle placement during IHD dramatically increases turbulent shear near the venous anastomosis, wall shear stress fluctuations increased from ~0.1 m/s to 0.4–0.7 m/s, 2 cm downstream of the needle tip, with turbulence intensities 5–6 times higher, indicating this may contribute potential endothelial injury and intimal hyperplasia and lead to AV graft complications.[902] Existing AV fistula/grafts were not designed for extended cannulation duration, and frequent manipulation may increase the risk of infection or access failure, which could jeopardize long-term dialysis options.[903] In addition, safe use of AV access for CRRT would require continuous bedside supervision.[904] For these reasons, dialysis catheters remain the preferred access for CRRT in both children and adults.

Practice Point 5.4.5: The decision on how to replace poorly performing uncuffed nontunneled dialysis catheters should be individualized. The options include a new venipuncture or, in select cases, a guidewire exchange of the existing dialysis catheter.

The performance of uncuffed nontunneled dialysis catheters is vital for the effective delivery of RRT. Inadequate blood flow rates or frequent circuit alarms can compromise dialysis efficiency, lead to treatment interruptions, and increase the risk of thrombosis and infection.[905] When dysfunction is confirmed and cannot be corrected through flushing, repositioning, or thrombolytic therapy, the catheter should be replaced**.** This may involve either a new venipuncture at a different site, which is preferred when feasible to minimize the risk of infection and mechanical complications, or a guidewire exchange of the existing catheter, which can be considered in select circumstances, particularly when vascular access is limited or when the patient is at high procedural risk.[876, 906-908]

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The 2011 Centers for Disease Control (CDC)/ Healthcare Infection Control Practices Advisory Committee (HICPAC) guidelines recommend caution with guidewire exchanges for central venous catheters, including dialysis catheters, due to the potential for increased infection risk.[909] When infection is suspected, the catheter should be completely removed, and if further access is required, a new catheter should be inserted at an alternative anatomical site.

Guidewire exchange may be appropriate in selected cases of non-infectious dysfunction, particularly when vascular access is limited or new venipuncture carries elevated risk.[876, 906, 908] In such cases, the procedure should be performed using strict aseptic technique. Additionally, if infection is suspected, the removed catheter tip should be submitted for microbiological analysis to aid diagnosis and guide treatment.[877, 909] Across all scenarios, adherence to standardized sterile protocols during catheter removal, replacement, or exchange remains essential to minimize infection risk and ensure safe vascular access management.[875, 896]

Practice Point 5.4.6: Do not perform routine or scheduled change of dialysis catheters to reduce the risk of catheter-related infection.

Multiple RCTs and observational studies have demonstrated that prophylactic catheter changes do not reduce infection rates compared to leaving catheters in place until no longer needed or a complication arises.[877, 910] Moreover, routine scheduled replacement introduces additional procedural risks, including mechanical complications such as arterial puncture, hematoma/bleeding, or pneumothorax, particularly in patients with coagulopathy; loss of available vascular access sites, especially in patients with limited central venous access options; and greater procedural burden and healthcare costs.[876, 909] These potential harms are particularly significant in critically ill patients, who often have impaired coagulation and require multiple concurrent therapies through central venous access. However, there are context-specific scenarios in which catheter replacement may be warranted. For example, femoral catheters may pose a higher infection risk, particularly in obese patients or those with elevated BMI, due to anatomical and hygiene-related factors.[874, 881] In such cases, early catheter replacement or site change may be appropriate, depending on duration of catheter use, patient mobility, and findings from infection surveillance. Ultimately, catheter replacement decisions should be individualized, guided by clinical assessment of risk factors, catheter site, patient characteristics such as BMI and mobility, and presence of complications.[874, 881, 911] A strategy that prioritizes clinical indications over routine replacement is aligned with evidence-based practice and promotes patient safety.[875]

Practice Point 5.4.7: In circumstances where prolonged indications for RRT are anticipated, a cuffed tunneled catheter can be considered when initiating RRT for AKI, particularly for children.

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Non-tunneled, uncuffed catheters are not ideal for long-term use. In clinical situations where prolonged RRT is anticipated or where preservation of central venous access is particularly important, the placement of a cuffed tunneled dialysis catheter may be appropriate, even in the acute setting. Cuffed tunneled catheters offer several advantages when extended use is expected. They are associated with lower rates of catheter-related bloodstream infections, owing to the presence of a subcutaneous tunnel and a Dacron cuff that facilitates tissue ingrowth and serves as a barrier to bacterial migration.[875, 911] Additionally, these catheters provide greater mechanical stability and reduce the risk of accidental dislodgement, which is especially beneficial in children.[912]

In children, the need to preserve central venous access is essential due to smaller vessel size and fewer available access sites. Repeated catheter replacements in children imposes risk and can present technical challenges, including increased likelihood of central venous stenosis, and cumulative procedural burden.[913] Therefore, early placement of a cuffed, tunneled catheter should be considered when resolution of AKI is uncertain or prolonged RRT is anticipated. Nonetheless, the decision to insert a tunneled catheter must consider the patient's clinical stability, procedural feasibility, and institutional resources, such as access to interventional radiology or surgical/interventional radiology teams. In unstable patients or in settings lacking fluoroscopic or surgical support, the use of a temporary non-tunneled catheter may still be necessary initially, with a plan for conversion once feasible.

Practice Point 5.4.8: For patients who remain dialysis dependent with low probability of resolution of AKI or patients being prepared for hospital discharge, transition to a cuffed tunneled catheter should be undertaken.

In the context of AKI, a subset of patients will remain RRT dependent and continue to require RRT at the time of hospital discharge. Prolonged use of a non-tunneled, uncuffed dialysis catheter has been linked to higher rates of catheter-related bloodstream infections, greater risk of mechanical complications, and poor long-term catheter function.[875, 877] Therefore, once it becomes evident that a patient will remain dialysis-dependent with a low likelihood of resolution of AKI in the short-term, or when discharge planning begins, transitioning to a cuffed tunneled catheter should be considered. These catheters offer greater stability and securement, reducing the risk of accidental dislodgement, and enhanced durability, making them suitable for outpatient dialysis or as a bridge to permanent access (i.e., AV fistula/graft). Furthermore, their use preserves central veins and minimizes long-term complications in patients who may progress to long-term dialysis.[914]

5.5. Anticoagulation for RRT

Recommendation 5.5.1: Where available, we recommend using regional citrate anticoagulation rather than heparin in children and adults receiving CRRT who do not have contraindications to citrate *(1B)*.

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Evidence shows that premature filter clotting can interrupt therapy, reduce efficacy, and increase bedside workload and costs of CRRT. As such, this recommendation places a high value on preservation of circuit patency to ensure optimal CRRT delivery, while minimizing the risk of circuit loss. It also places high value on balancing the benefits of anticoagulation with the risk of adverse events due to anticoagulation, including bleeding and need for blood transfusions. Note this recommendation applies to patients who are not receiving systemic anticoagulation for other indications (e.g., venous thromboembolism, atrial fibrillation).

Key information

Balance of benefits and harms

The use of anticoagulation during CRRT for patients with AKI who are not already receiving systemic anticoagulation improves and preserves circuit patency and extends filter lifespan, which reduces treatment interruptions and associated complications. In patients with high bleeding risk, anticoagulation with unfractionated heparin may pose a significant hazard.

A systematic review of 6 RCTs comparing regional citrate anticoagulation (RCA) with unfractionated heparin (UFH) showed that UFH increased the risk of both premature filter clotting (RR: 1.70; 95% CI: 1.09–2.65) and bleeding events (RR: 3.09; 95% CI: 2.08–4.60) with no evidence of a difference in discontinuation due to other adverse events (Supplementary Table S88).[915] Another systematic review of 3 RCTs comparing RCA with regional UFH showed no difference in the risk of filter clotting (RR: 1.01; 95% CI: 0.61–1.67) with an uncertain effect on bleeding risk (RR: 1.82; 95% CI: 0.23–14.43; Supplementary Table S89).[915]

RCTs investigating low molecular weight heparin (LMWH) versus RCA showed that use of RCA greatly decreased the risk of major bleeding and discontinuation due to adverse events, without evidence of a difference in filter clotting (Supplementary Table S90).[915, 916]

In a network meta-analysis, RCA in critically ill participants was associated with significantly longer filter life (weighted mean difference [WMD] +23 hours; $p<0.001$) and lower bleeding risk than both UFH and no anticoagulation.[915]

For circuit anticoagulation in children, systematic review of 6 RCTs comparing RCA with UFH concluded that use of RCA reduced the risk of systemic bleeding (RR: 0.80; 95% CI: 0.35–1.85) compared with UFH, with uncertain effects on filter clotting (Supplementary Table S91). A different systematic review evaluated 1706 pediatric CRRT sessions across 11 studies, of which 38% utilized RCA and 62% used systemic UFH.[917] Regional citrate anticoagulation was consistently associated with significantly longer circuit life and a reduced risk of clotting, with a pooled risk difference for filter clotting of –20.4% (95% CI: –14.4% to –26.5%) compared to UFH. Although survival rates did not differ significantly

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across most studies, RCA demonstrated a more favorable profile in reducing the need for circuit changes and red blood cell transfusion.[918-921]

Certainty of evidence

There is moderate certainty of evidence, in adults, that, compared with RCA, systemic UFH increases the risk of both premature filter clotting and bleeding events, with no evidence of a difference in discontinuation due to other adverse events. The certainty of evidence was downgraded due to methodological limitations, but the certainty for the bleeding outcome was upgraded due to a large effect size.

There is low certainty of evidence that regional UFH, in adults, has no difference in the risk of filter clotting, with an uncertain effect on bleeding, compared with RCA. The certainty was downgraded for methodological quality and imprecision of estimates of effect.

There is also high certainty of evidence that, compared with LMWH, RCA greatly decreases the risk of major bleeding and discontinuation due to adverse events, with very low certainty of evidence regarding a difference in filter clotting. There were methodological limitations of the studies, but the certainty for harm from bleeding and for discontinuation due to adverse events were upgraded due to large estimates of effect. Given the high certainty of evidence for adverse events, but very low certainty of evidence of benefits, overall, it was determined that there is low certainty of evidence regarding RCA versus LMWH.

There is very low certainty of evidence for the comparison of RCA and regional UFH in children. Certainty of evidence was downgraded for methodological limitations, sparseness of studies, imprecision, and inconsistencies pertaining to filter clotting.

Values and preferences

The Work Group perceived that both patients and healthcare professionals would prefer anticoagulation strategies that preserve circuit patency to ensure adequate solute clearance, ultrafiltration, mitigation of interruptions, and minimization of adverse events (e.g., bleeding events, metabolic complications; need for transfusion). Preservation of circuit lifespan will also reduce bedside nursing workload, result in fewer dialysis catheter manipulations, enable delivery of the prescribed RRT dose-intensity, and reduce the amount of waste. At the same time, there was a strong perception for preferentially using an anticoagulation regimen that would minimize the risk of bleeding events, particularly among patients with increased risk (e.g., liver disease; recent surgery; coagulopathy; thrombocytopenia, etc.). This demands that healthcare professionals balance the relative benefits of anticoagulation (e.g., longer filter lifespan) with the potential for adverse events. Among those at high bleeding risk, use of anticoagulant strategies with a lower risk of bleeding or no anticoagulation may be preferable, despite the expectation of shorter circuit lifespan. Preferences may also be shaped by institutional expertise, availability of specific anticoagulants, clinician experience with protocols, and ability to implement appropriate

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monitoring procedures.[922] For example, RCA may be preferred in centers with adequate training and infrastructure, whereas UFH remains commonly used due to its familiarity and relative ease of administration.

Among pediatric intensivists and nephrologists, the preference for RCA is particularly strong due to the frequent use of small circuits and low blood flow rates, which predispose to clotting when no or suboptimal anticoagulation is used.[923-925]

Resource use and costs

The use of anticoagulants in CRRT has important implications for resource utilization and healthcare costs, particularly in lower resource settings. Prolonging circuit life through effective anticoagulation reduces the frequency of circuit changes, which can in turn lower the consumption of CRRT consumables, reduce nursing workload, and reduce waste.[922] Each circuit replacement not only incurs material costs but also requires significant clinician time and interrupts treatment delivery. Regional citrate anticoagulation, while associated with longer filter lifespan and improved circuit patency, requires additional resources due to more complex protocols, including clinician education and monitoring of circuit, factors that may limit its implementation in some institutions.[926] Unfractionated heparin remains widely used due to its familiarity, ease of administration, and relatively low costs, but higher rates of circuit failure and bleeding-related complications may increase downstream costs, including transfusions and circuit replacement.[916] This is very relevant, in particular in low-resource settings, where costs associated for CRRT may be limited.

Regional citrate anticoagulation, though more complex to administer than UFH, may ultimately offer favorable resource utilization by prolonging filter lifespan, reducing circuit changes, and minimizing bleeding-related complications. Evidence supports that RCA increases filter life by 17–23 hours on average compared to UFH, which translates into fewer interruptions, reduced nursing workload, and less blood loss.[915, 924, 927-930] This will reduce need to replace circuits, for blood transfusions, and emergent catheter manipulations, all important cost drivers for CRRT.

Considerations for implementation

The successful implementation of anticoagulation protocols in CRRT is influenced by institutional infrastructure, local expertise, monitoring capabilities, and drug availability.[931] Regional citrate anticoagulation results in superior filter life and bleeding risk reduction,[915, 922] but requires dedicated protocols, calcium and acid-base monitoring, and trained personnel to manage metabolic complications such as citrate accumulation or dysnatremia.[915] These requirements may be challenging in low-resource settings, which limits broader adoption despite its clinical advantages.[931] In contrast, UFH is widely available and used due to its familiarity, ease of use, and relatively low cost,[931] though it carries a higher risk of bleeding and variable circuit lifespan.[916, 931] In low-resource settings, some centers continue to operate

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CRRT without anticoagulation despite shorter circuit life, due to safety concerns and cost constraints.[931]

For successful implementation, institutions should develop standardized protocols, ensure availability of necessary monitoring tools, and provide regular training for clinical staff. Tailoring anticoagulation strategy to patient-specific bleeding risk, institutional capability, and cost-effectiveness is essential to optimize CRRT delivery across diverse care settings.

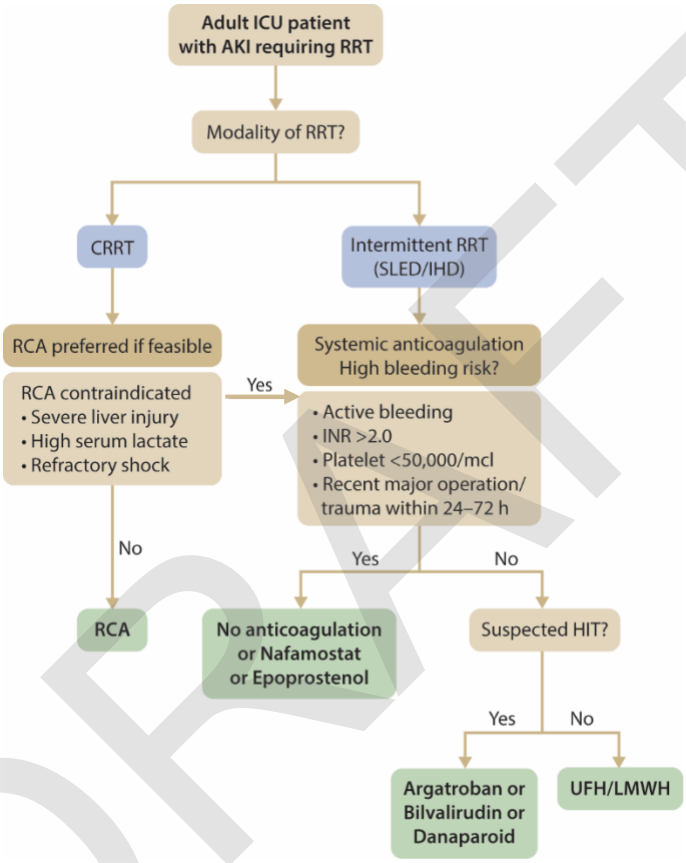

Figure 17 | Anticoagulation strategy in a patient with AKI requiring RRT (CRRT/SLED/IHD). AKI, acute kidney injury; CRRT, continuous renal replacement therapy; HIT, heparin-induced thrombocytopenia; ICU, intensive care unit; IHD, intermittent hemodialysis; INR, international normalized ratio; LMWH, low-molecular weight heparin; RCA, regional citrate anticoagulation; RRT, renal replacement therapy; SLED, sustained low-efficiency dialysis; UFH, unfractionated heparin

Circuit anticoagulation should be applied using institutional protocols and procedures, considering the individual patient risk of bleeding, coagulation profile, metabolic tolerance, along with clinician expertise and resource availability (Table 50).

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Rationale

The rationale for using anticoagulation in CRRT is to prevent premature or unplanned circuit loss and to optimize filter lifespan and effective treatment time. In patients not receiving systemic anticoagulation, the addition of anticoagulant prolongs circuit lifespan, reduces clotting events, and improves the delivery of prescribed RRT therapy. Conversely, the absence of anticoagulation often leads to circuit clotting, increased blood loss from discarded circuits, and interruptions in therapy. Based on current data, use of RCA is recommended over UFH in children and adults who do not have contraindications to citrate.

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Table 50 | Summary of the pharmacokinetics profiles of anticoagulants used to maintain circuit patency in CRRT

Anticoagulant	Molecular weight	Mechanism	Dose	Route/dose	Onset of action	Clearance	Monitoring	Pros	Cons	Contraindication	Notes
Regional citrate	192 Da (trisodium citrate; dilute citrate; ACD-A)	Chelates Ca, inhibits clotting in circuit (regional)	Citrate 3–4 mmol/l blood flow; Ca 0.25–0.5 mmol/l postfilter	Prefilter citrate infusion, Ca infusion postfilter	Immediate; half-life 5–10 min	Hepatic metabolism, muscle	Ionized Ca (pre/post), total Ca, HCO3-, pH, lactate	Prolongs filter life; minimal systemic bleeding; safe in high-bleed risk	Requires close monitoring; risk of alkalosis or citrate accumulation	Severe liver failure; shock with high vasopressors; citrate accumulation	Requires institutional infrastructure and trained staff
Unfractionated heparin	3000–30,000 Da	Enhances antithrombin III activity → inhibits thrombin & factor Xa	Bolus 500–1000 IU then infusion 5–10 IU/kg/h (adjust aPTT or anti-Xa)	Systemic or prefilter bolus with infusion, titrate to aPTT or anti-Xa	Minutes; half-life 1–2 h	Hepatic metabolism, some kidney	aPTT, ACT, anti-Xa	Simple to use; widely available; low-cost	Systemic bleeding risk; HIT risk; variable effect	HIT; high bleeding risk	Most common globally; variable filter life
Low molecular weight heparin	~4000–6000 Da	Inhibits factor Xa (primarily) via antithrombin	40–60 IU/kg SC or 1 mg/kg i.v. bolus predialysis	SC or bolus iv, fixed dose per weight	3–5 h (SC); half-life 4–7 h	Kidney	Anti-Xa (optional)	Predictable PK; less HIT risk than UFH	Kidney accumulation; less reversible	HIT, severe kidney failure	Less used in CRRT due to long half-life
Nafamostat mesylate	539 Da	Synthetic serine protease inhibitor, short half-life	0.2–0.5 mg/kg/h continuous infusion (no bolus needed)	Continuous infusion in circuit	Immediate; half-life 8 min	Rapid plasma hydrolysis	Minimal, observe for clotting/ bleeding	Low bleeding risk; short-acting; ideal for high-bleed risk	Expensive; limited availability outside East Asia	Hypersensitivity; cost/access issues	Used widely in Japan/South Korea
Argatroban	526 Da	Direct thrombin inhibitor	Starting 0.5–1 µg/kg/min iv, titrate to aPTT target	i.v. infusion, titrate to aPTT	Immediate; half-life 45 min	Hepatic metabolism	aPTT, liver function	Safe in kidney failure; effective in HIT	Costly; required careful titration	Severe liver dysfunction	Preferred in HIT with RRT
Bivalirudin	2180 Da	Direct thrombin inhibitor	Starting 0.03–0.1 mg/kg/h, adjust for kidney function	i.v. infusion, titrate to aPTT	Immediate; half-life 25 min	Kidney and enzymatic	aPTT, kidney function	Short half-life; effective in HIT	Kidney accumulation; high cost	Severely abnormal kidney function	Fewer data in CRRT; dosing may need adjustment

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Epoprostenol	360 Da	Inhibits platelet aggregation	4–10 ng/kg/min i.v. infusion, titrate as tolerated	i.v. infusion	Immediate; half-life 3–6 min	Very short half-life (minutes)	Clinical bleeding, hemodynamics	Platelet inhibition without systemic effect; minimal bleeding	Hypotension, tachyphylaxis; vasodilation	Uncontrolled hypotension	Rarely used; requires close BP monitoring

ACT, activated clotting time; ACDA, acid-citrate-dextrose solution A; aPTT, activated partial thromboplastin time; BP, blood pressure; Ca, calcium; CRRT, continuous renal replacement therapy; HCO3-, bicarbonate; HIT, heparin-induced thrombocytopenia; i.v., intravenous; PK, pharmacokinetics; RRT, renal replacement therapy; SC, subcutaneous; UFH, unfractionated heparin

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Practice Point 5.5.1: Unfractionated heparin, epoprostenol, or nafamostat mesylate are acceptable alternatives to regional citrate anticoagulation for children and adults receiving CRRT if citrate is contraindicated or not available.

In clinical scenarios where RCA cannot be used, due to contraindications (e.g., severe liver disease, shock states) or logistical barriers, alternative anticoagulation strategies can be employed to maintain CRRT circuit patency while minimizing the risk of complications (e.g., bleeding).

Unfractionated heparin remains a commonly used alternative. However, in patients at increased bleeding risk, its use must be weighed carefully due to the well-documented risk of major hemorrhage with systemic anticoagulation and heparin-induced thrombocytopenia (HIT). For such patients, nafamostat mesilate (a synthetic serine protease inhibitor) and epoprostenol (a synthetic prostacyclin) have been suggested as safe and effective alternatives. Two RCTs in adults receiving CRRT support the efficacy and safety of nafamostat mesylate in high bleeding risk populations.[932, 933] Choi *et al.* performed a RCT of 51 participants receiving CRRT at a high risk of bleeding, where nafamostat mesilate was found to reduce clotting events without increasing bleeding complications compared to no anticoagulation.[932] Lee *et al.* studied 73 adults receiving CRRT and found use of nafamostat mesilate resulted in fewer clotting events (1.15 vs. 1.74 circuits/24 hours, $P<0.05$) and required use of fewer filters (2.7 vs. 4.5 per patient, $P=0.01$) compared to those receiving no anticoagulation.[933] These findings and a recent systematic review support nafamostat mesilate as an alternative anticoagulant where RCA and UFH are contraindicated or unavailable.[934]

In children receiving CRRT, several studies demonstrate feasibility and safety of alternative anticoagulation.[924, 935] Miyaji *et al.* retrospectively compared RCA and nafamostat mesilate in critically ill children receiving CRRT.[935] Both groups achieved effective anticoagulation with no significant differences in major bleeding, suggesting comparable safety profiles.[935] The Worldwide Exploration of Renal Replacement Outcomes Collaborative in Kidney Disease (WE-ROCK) multinational registry included over 800 children and young adults on CRRT.[936] Although anticoagulation strategies varied, centers with experience using nafamostat mesilate or prostacyclin reported comparable survival and filter longevity across strategies.[937] Haga *et al.* reported that 40% of Japanese pediatric ICUs surveyed routinely used nafamostat mesilate as the primary anticoagulant for pediatric CRRT, reflecting national clinical acceptance in high bleeding risk patients.[938]

Epoprostenol, a platelet inhibitor with vasodilatory effects, is another alternative used in both children and adults, especially when systemic anticoagulation is undesirable. While high-quality RCT data are limited, its use has been supported by clinical experience and observational data.[918, 921, 939]

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Practice Point 5.5.2: The addition of regional citrate anticoagulation to systematic anticoagulation can be appropriate for children and adults with hypercoagulable states receiving CRRT.

Patients with systemic hypercoagulable states, such as severe COVID-19, nephrotic syndrome, or systemic inflammatory conditions can experience recurrent circuit clotting during CRRT, despite receiving systemic anticoagulation. In such scenarios, the addition of RCA to ongoing systemic anticoagulation may enhance filter longevity without increasing bleeding risk and thus be a reasonable strategy in selected children and adults.

A prospective multicenter study by Helms *et al.* involving critically ill patients with COVID-19 and acute respiratory distress syndrome reported a high incidence of thrombotic complications (up to 69%)**,** even in patients already receiving systemic prophylactic or therapeutic anticoagulation.[940] This underscores the need to consider augmented anticoagulation strategies for selected patients expressing hypercoagulable states receiving extracorporeal therapies.

A retrospective cohort study by Valle *et al.* evaluated 238 ICU patients with COVID-19-associated AKI undergoing CRRT and compared outcomes between RCA alone and RCA plus UFH.[941] The combined anticoagulation approach resulted in a ~60% reduction in the hazard of filter clotting, without a significant increase in bleeding events.[941] Similar findings were reported in non-COVID hypercoagulable states. In patients with nephrotic syndrome**,** Wang *et al.* demonstrated that the addition of LMWH to RCA during CRRT was effective in maintaining circuit patency, with no increase in bleeding complications.[942] In critically ill children, Zhu *et al.* retrospectively evaluated whether either RCA alone or in combination with low-dose UFH was effective for preserving and prolonging filter lifespan.[943] The study found that the combined strategy improved circuit survival time without increasing hemorrhagic risk, reinforcing the potential safety and benefit of dual anticoagulation in hypercoagulable pediatric patients.[943] These results suggest there may be a synergistic effect between systemic and regional anticoagulation in preventing premature circuit loss in hypercoagulable patients receiving CRRT.

Practice Point 5.5.3: Unfractionated or low-molecular-weight heparin should be considered for children and adults receiving intermittent hemodialysis (IHD) or PIRRT without increased bleeding when not already receiving systematic anticoagulation.

Unfractionated heparin and LMWH are widely used anticoagulants during conventional IHD or PIRRT to prevent clotting of the extracorporeal circuit. Their use is particularly relevant in patients who are not receiving systemic anticoagulation and do not have an elevated bleeding risk.

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A study by Mareedu *et al.* in adult patients with COVID-19 associated AKI undergoing PIRRT found that LMWH was superior to UFH in preventing extracorporeal circuit clotting, with a lower incidence of filter clotting events and comparable bleeding risk.[944] LMWH may be preferable due to more predictable pharmacokinetics and lower clotting rates, but both are acceptable and widely available anticoagulation options. While flush-only (saline) protocols may be used in patients at high bleeding risk, they are generally associated with a higher risk of circuit clotting and treatment interruption and increase the workload of the clinical staff.

Further supporting evidence comes from a large observational analysis of patients receiving IHD and concomitant systemic antiplatelet or anticoagulant therapy.[945] The findings suggest that the use of intradialytic UFH did not significantly increase bleeding events**,** even in patients on concurrent antiplatelet agents, and remained effective in preserving circuit patency.[945] This highlights the safety of UFH under routine conditions and provides reassurance for its use in patients without overt bleeding risk. Although pediatric-specific evidence is more limited, clinical practice patterns align with adults, with UFH being routinely used in IHD and PIRRT for children, particularly those with stable hemodynamics and low bleeding risk.

Practice Point 5.5.4: Anticoagulation with argatroban, danaparoid, or bivalirudin, rather than other non-heparin anticoagulants, should be used in adults receiving RRT with acute heparin-induced thrombocytopenia (HIT) who require systemic anticoagulation.

HIT is a serious immune-mediated complication of heparin therapy that necessitates immediate cessation of all heparin products and transition to alternative anticoagulation. For patients receiving RRT, choosing an effective and safe non-heparin anticoagulant is essential to minimize thrombotic risk and maintain circuit patency. Argatroban appears to offer the most favorable balance of efficacy and safety, with danaparoid and bivalirudin also considered acceptable alternatives.

Argatroban, a direct thrombin inhibitor metabolized by the liver, has been widely studied in patients with HIT requiring RRT.[946] A retrospective cohort study of 74 patients receiving CRRT with suspected HIT found that argatroban and bivalirudin were both effective, but argatroban had more activated partial thromboplastin time (aPTT) levels within the therapeutic range, indicating better dosing control.[946] In a RCT of 66 participants receiving CRRT with suspected HIT, argatroban was compared with lepirudin.[947] Although both anticoagulants were found to result in similar filter patency, argatroban was associated with significantly fewer clinically relevant bleeding events (4 vs. 11; OR: 3.9; 95% CI: 1.1–14.0; P=0.040).[947]

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A Bayesian network meta-analysis evaluated various non-heparin anticoagulant regimens for patients with HIT and suggested that argatroban was associated with the lowest risk of bleeding and thromboembolism, as well as potentially lower mortality and shorter hospital stays compared with alternatives, including danaparoid, lepirudin, and bivalirudin.[948]

Danaparoid, an indirect factor Xa inhibitor with minimal cross-reactivity to heparin-antibodies against platelet factor 4 (PF4), also has evidence supporting its use. In a case-series by Magnani *et al.* of 122 patients receiving RRT, danaparoid was found effective in maintaining RRT circuit patency with low rates of bleeding complications.[949] Bivalirudin, another direct thrombin inhibitor, has also been used in RRT, although its renal clearance necessitates dose adjustments. In comparative studies, bivalirudin has shown similar efficacy and bleeding risk to argatroban but may be less preferred in patients with severely abnormal kidney function due to the risk of accumulation.[950]

Practice Point 5.5.5 Regional citrate anticoagulation rather than heparin or non-heparin anticoagulants is preferable in adults receiving RRT with subacute (HIT-A, HIT-B) or remote HIT, who are not receiving systemic anticoagulation and require anticoagulation to prevent clotting of the dialysis circuit.

In patients with a history of HIT, particularly those with subacute or remote HIT who no longer require systemic anticoagulation, the risk of HIT recurrence remains a concern if heparin is reintroduced. Additionally, non-heparin anticoagulants used systemically may increase bleeding risk or require complex dosing adjustments. In this context, RCA offers a safe and effective strategy for maintaining circuit patency during RRT without exposing the patient to systemic anticoagulation risks.

The American Society of Hematology (ASH) 2018 Guidelines explicitly recommend the use of RCA over heparin or other systemic non-heparin anticoagulants in this scenario.[951] For patients with subacute HIT A, subacute HIT B, or remote HIT undergoing RRT and not requiring systemic anticoagulation, the ASH Guideline panel issued a conditional recommendation favoring RCA**,** despite very-low certainty of evidence, due to its favorable safety profile and lack of systemic anticoagulant effect. The guideline emphasized that RCA is not appropriate in acute HIT, where systemic anticoagulation is still needed.[951]

5.6 Hemofilters for RRT

Practice Point 5.6.1: Biocompatible membrane hemofilters and dialyzers should be used in children and adults with AKI undergoing CRRT or IHD.

All modern hemodialyzers and filters are hollow-fiber devices constructed with membranes made from cellulose, modified cellulose, or synthetic polymers like polysulfone and polyethersulfone. Their core function is to clean blood by removing solute and water through the membrane. While water removal relies on membrane hydraulic permeability, this

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is no longer a limiting factor clinically due to automated ultrafiltration control systems, which prevents excessive fluid removal. Consequently, manufacturers have shifted focus toward optimizing membranes for enhanced solute exchange efficiency by increasing pore size (e.g., high-flux membranes defined by β_2-microglobulin clearance >20 ml/min) and engineering membrane surface area, fiber geometry, and material properties to boost diffusive, convective, adsorptive clearance.[952]

Most modern biocompatible membranes are synthetic and include materials such as polysulfone, polyethersulfone, polyamide, polycarbonate, polyacrylonitrile (PAN), polymethylmethacrylate (PMMA), and AN69, a copolymer of sodium methallyl sulfonate and acrylonitrile (Table 51).[953] These membranes are designed to minimize complement activation and cytokine release, thereby reducing inflammation and improving patient tolerance during RRT.

Table 51 | Summary of hemofilter membrane materials

Membrane material	**Composition**	**Key properties**	**Advantages**
Polysulfone (PSU)	Aromatic polymer with sulfone groups	- High flux - Good biocompatibility - Thermostable	- Durable, low protein binding
Polyethersulfone (PES)	Similar to PSU, but with ether linkages	- Excellent permeability - Chemically stable	- Supports high-volume exchange
Polyamide	Aromatic-aliphatic copolyamide blended with hydrophilic polyvinylpyrrolidone (PVP)	- Hydrophilic - Moderately biocompatible	- Good for low-protein binding
Polyacrylonitrile (PAN) Acrylonitrile 69 (**AN69)**	Acrylonitrile polymer	- High adsorption - Negative surface charge (Risk of bradykinin release)	- Effective for cytokine/cationic molecule binding by adsorptive capacity
Polymethylmethacrylate (PMMA)	Acrylic resin	- High adsorptive capacity - Hydrophobic -Uniform homogenous pore size	- Binds middle molecules & cytokines by adsorptive capacity

The acrylonitrile 69 (AN69) membrane and its surface-treated variants (e.g., AN69ST) have demonstrated favorable biocompatibility and cytokine adsorption properties.[953, 954] There remains uncertainty on the efficacy of the AN69 membrane to prolong circuit/hemofilter lifespan and this may be dependent on patient characteristics, clinical circumstances, and parameters of RRT (e.g., modality). Surface-modified PAN membranes, such as polyethyleneimine-treated hemofilters, have been explored for their potential benefit in the setting of anticoagulation-free PIRRT.[955] A randomized crossover study in 60 acutely ill adults at high risk of bleeding compared heparin-primed polyethylenimine-treated AN69 membrane (AN69ST) versus AN69 membranes on the

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success of RRT, filter lifespan, and severity of filter clotting, along with factors associated with premature filter clotting.[955] The success rate, filter lifespans, and severity of filter clotting were not significantly different. However, in multivariable analysis, higher platelet count, and higher serum hemoglobin level were associated with increased clotting risk, whereas a lower aPTT was associated with longer filter lifespan. In patients with aPTT <35.3 seconds, serum hemoglobin >83 g/l, and platelet count $<70\times10^9$/l, the AN69ST was associated with longer filter lifespan by 252 minutes, suggesting potential benefit in select subgroups.[955] Comparative studies, such as those evaluating AN69 ST100 versus oXiris® membranes in non-anticoagulated patients with liver failure receiving CRRT suggest similar or modest differences in hemofilter longevity in adult patients.[953, 954]

PMMA membrane dialyzers, first introduced in 1977, continue to hold a unique place in modern dialysis practice due to their distinctive adsorption properties and biocompatibility. PMMA membranes are characterized by a uniform pore structure and the ability to adsorb middle- and large-molecular weight proteins, making them particularly effective for patients with inflammatory or uremic symptoms. Successive generations of PMMA dialyzers, such as the BG, BK-F, and NF models have been refined to improve pore size, antithrombogenicity, and overall hemocompatibility.[956]

Their protein-adsorptive capacity, improved biocompatibility, and potential to alleviate dialysis-related symptoms and enhance immune response make them a valuable option for selected patient populations. Overall, the use of biocompatible synthetic membranes is considered standard of care and contributes to safer, more effective RRT in acutely ill patients.

Practice Point 5.6.2: Non-pharmacologic strategies that may be used to maintain and maximize circuit/hemofilter lifespan include optimizing catheter position in the right atrium, use of predilution hemofiltration, and continuous venovenous hemodialysis (CVVHD) or hemodiafiltration (CVVHDF) rather than continuous venovenous hemofiltration (CVVH).

Maintaining hemofilter and circuit patency is a key goal in CRRT, where interruptions due to circuit disruption can compromise solute clearance and ultrafiltration. In addition to pharmacologic anticoagulation, several non-pharmacologic strategies can optimize circuit lifespan, especially when anticoagulation is contraindicated or must be minimized.[957] Optimizing predilution strategies, catheter positioning, and CRRT modality are nonpharmacological strategies that may enhance circuit survival (Table 52). These measures are especially relevant in postoperative or bleeding-prone patients where anticoagulants may be associated with bleeding risk or are contraindicated.

Tsujimoto *et al.* evaluated a spectrum of non-pharmacological interventions to prevent or mitigate premature clotting of extracorporeal circuits during CRRT (Table 52).[957]

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This systematic review found that use of CVVHD or CVVHDF rather than CVVH significantly increased circuit lifespan by an average of 10.15 hours (95% CI: 5.15–15.15). Similarly, use of predilution hemofiltration rather than post-dilution was associated with a mean increase in filter lifespan of 9.34 hours (95% CI: -2.60 to 21.29). Catheter-related factors played a significant role, and surface-modified double-lumen catheters increased circuit duration by 16.0 hours (95% CI: 13.49–18.51). Notably, hemofilters designed with a greater number of shorter hollow fibers were associated with a reduced circuit life of 5.87 hours (95% CI: -10.18 to -1.56).[957]

Catheter position is also essential to maintain circuit patency. Studies show that proper positioning of the catheter tip in the right atrium improves blood flow dynamics and reduces recirculation, which may prolong filter lifespan and improve dialysis efficiency.[958, 959] In an RCT of 100 critically ill adult participants, Morgan *et al.* compared long (20–24 cm) versus short (15–20 cm) soft silicone catheters for CRRT targeting tip placement in the right atrium versus in the superior vena cava.[958] Longer catheters placed in the right atrium were shown to significantly prolong mean circuit lifespan by 6.5 hours (median 24 h; IQR: 11–32 vs. 17.5 h; IQR: 8–23; P=0.001).[958] Additionally, these longer catheters improved the delivered/prescribed daily RRT dose-intensity to a median of 91% (IQR: 85%–100%) compared to 81% (IQR: 72%–97%) with shorter catheters (P<0.001), reduced the number of clotting events per patient from 3.6 to 2.3 (P=0.04), and decreased access-related circuit failures per patient from 0.53 to 0.19 (P=0.04).[958] Placement in the right atrium did not significantly increase complications, with similar rates of atrial arrhythmias between groups (28% vs. 21%, P=0.6).[958]

The prescribed blood flow rate during CRRT varies globally in adults, ranging from 80 ml/min to over 300 ml/min.[959-961] Evidence from 2 RCTs involving a total of 134 participants receiving CRRT found that higher blood flow rates (200–250 ml/min vs. 100–150 ml/min) had little or no impact on circuit lifespan compared to standard rates.[957, 962, 963]

Various synthetic membranes have been investigated, such as AN69, AN69ST, and oXiris® (heparin-grafted membrane), for their capacity to preserve circuit patency and reduce clotting through enhanced biocompatibility or cytokine adsorption. However, current evidence does not support a clear advantage of any specific membrane type for preserving and prolonging filter lifespan or improving clinical outcomes in patients receiving CRRT without anticoagulation.[954, 964, 965,966]

Table 52 | Nonpharmacological interventions investigated in RCTs to prevent clotting during CRRT

Interventions	Number of trials	Number of participants	Comment
Modes			
CVVH, CVVHD, or CVVHDF[967, 968]	2	62	The mean circuit lifespan with CVVHDF was 10.2 hours longer (95% CI: 5.2–15.2) than CVVH.

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Predilution or post-dilution[969, 970]	2	47	Increase in filter lifespan of 9.34 hours (95% CI: -2.60 to 21.29) with predilution.
Blood flow			
Higher or standard blood flow rate[962, 963]	2	134	No significant difference of filter lifespan.
Catheter types			
Catheter length (long or short)[958]	1	100	The mean circuit lifespan with longer catheters was 6.5 hours longer (95% CI: 1.5–11.5) than short catheters
Surface-modified double-lumen catheter[971]	1	262	The mean circuit lifespan with surface-modified double-lumen catheters was 16 hours longer (95% CI: 13.5–18.5) than standard double-lumen catheters.
Filter types			
AN69ST with heparin-grafted membrane[954, 965]	2	40	No significant difference of filter lifespan.
Longer or shorter hollow fiber[972]	1	6	The mean circuit lifespan with longer fiber filters had longer running times (1276 vs. 851 min, *P*=0.04) than standard hollow fiber filters
Flat plate fiber or hollow fiber[a]	1	38	No significant difference of filter lifespan.
Filter with a larger membrane surface area[a]	1	38	No significant difference of filter lifespan.
Other			
Single- or double-site infusion anticoagulation[a]	1	38	No significant difference of filter lifespan.

[a] From one study embedding 3 comparisons.[966] AN69ST, polyethylenimine-treated AN69 membrane; CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; RCT, randomized controlled trial. Adapted from a Cochrane systematic review.[957]

Practice Point 5.6.3: Where regional citrate or systemic heparin anticoagulation are contraindicated or not available, priming of the CRRT circuit/filter with a solution containing unfractionated heparin (UFH) may be used to increase circuit/hemofilter lifespan.

Priming the circuit with UFH can theoretically precoat the hemofilter surfaces and tubing and mitigate early thrombus formation by inhibiting platelet and fibrin adhesion. While the use of regional or systemic anticoagulation (e.g., RCA) often yields longer filter survival, the use of heparin priming can provide a pragmatic and low-risk alternative, especially for patients with contraindications to RCA or where bleeding risk limits the use of systemic heparin.[973]

Several studies have evaluated the efficacy of heparin-albumin priming to reduce extracorporeal circuit clotting during RRT, suggesting this strategy may have a potential role in prolonging circuit lifespan and reducing exposure to systemic anticoagulation. In an *in*

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vitro study by Kyrk *et al.,* circuits primed with a combination of 5,000 IU of unfractionated heparin and albumin (5 ml of 20% solution in 1l saline) were able to complete the full 192-minute simulated hemodialysis sessions with only minimal clotting.[974] In contrast, circuits primed with 0.9% saline alone clotted within a median of 21 minutes (IQR: 18–27 minutes), and those with albumin alone lasted a median of 26 minutes (IQR: 19–35 minutes), implying the potential superior thrombo-prophylactic effect of the heparin-albumin combination.[974]

Limited clinical evidence from retrospective analyses supports these findings. In a retrospective cohort study of 321 patients with high bleeding risk receiving 1408 IHD sessions, use of heparin-albumin priming was associated with a clotting-related session interruption rate of 1.0% compared to 0.8% in those receiving standard heparin.[975] Importantly, patients in the heparin-albumin group required significantly lower systemic heparin doses, median 1200 IU compared to 5000 IU (P<0.001), with no increase in bleeding complications.[975] In a similar retrospective cohort study of 68 patients receiving IHD (248 sessions), use of a priming solution with heparin-albumin was associated with lower utilization of heparin during IHD, with no increase in clotting or bleeding complications when compared with use of systemic anticoagulation.[976]

5.7. Replacement and dialysate solutions for RRT

Practice Point 5.7.1: Use bicarbonate, rather than lactate, as a buffer in dialysate and replacement fluid for CRRT in adults with AKI in the following scenarios: circulatory shock, liver failure or lactic acidemia.

This practice point is reformatted from Recommendation 5.7.1 from the KDIGO 2012 Guideline.[12] The guidance is based on avoiding metabolic acidosis and improving hemodynamic stability of patients with conditions that may impair lactate metabolism. Evidence from RCTs consistently shows superior metabolic and hemodynamic effects with the use of bicarbonate-buffered compared with lactate-buffered solutions for patients receiving CRRT.

Bicarbonate-buffered solutions are preferred due to their superior metabolic compatibility in critically ill patients with impaired lactate metabolism. In circulatory shock, hepatic perfusion is often reduced, impairing the capacity of the liver to convert lactate into bicarbonate. Consequently, the use of lactate-buffered solutions may result in iatrogenic lactate accumulation and worsen metabolic acidosis. In contrast, bicarbonate-buffered fluids provide more predictable acid-base correction and avoid iatrogenic lactic acidosis, leading to improved hemodynamic tolerance and more accurate interpretation of serum lactate concentrations as a measure of end-organ perfusion.[977]

Four notable RCTs support the use of bicarbonate over lactate as a buffer in CRRT. In a single center RCT by Barenbrock *et al.*, the use of bicarbonate-buffered replacement fluids in participants undergoing CVVH significantly improved cardiovascular stability

compared to lactate-buffered replacement fluids.[978] Among the 117 critically ill adults enrolled, those receiving bicarbonate-buffered solutions had lower mean blood lactate levels (17.4 ± 8.5 mg/dl) compared to the lactate-buffered group (28.7 ± 10.4 mg/dl; $P<0.05$), and higher serum bicarbonate concentrations (23.7 ± 0.4 mmol/l vs. 21.8 ± 0.5 mmol/l; $P<0.01$). Importantly, the incidence of hypotensive episodes was significantly lower in the bicarbonate-buffered group (0.26 ± 0.09 episodes per 24 h) compared to the lactate-buffered group (0.60 ± 0.31; $P<0.05$). Furthermore, cardiovascular events occurred less frequently in participants treated with bicarbonate-buffered fluids (15% vs. 38%; $P<0.01$).[978]

Similarly, in the study by Kierdorf *et al.*, 12 adults with AKI receiving CVVH were enrolled in a randomized crossover trial comparing bicarbonate- versus lactate-buffered replacement fluids.[979] The findings suggested that bicarbonate-buffered solutions provided superior acid-base balance and hemodynamic stability. Specifically, participants receiving bicarbonate-buffered solutions had significantly higher arterial pH values (mean 7.38 ± 0.04) compared to those receiving lactate buffers (7.32 ± 0.06; $P<0.05$), and serum bicarbonate levels were also higher (22 ± 3 mmol/l vs. 18 ± 4 mmol/l; $P<0.05$). Importantly, the bicarbonate-buffered group experienced fewer hypotensive episodes (0.8 ± 0.7 vs. 2.3 ± 1.1 episodes/day; $P<0.05$) and lower systemic lactate levels, particularly in the context of impaired tissue perfusion.[979]

In a prospective, randomized crossover trial involving 26 critically ill adults undergoing CVVHD, Zimmerman *et al.* directly compared a bicarbonate-buffered dialysate with a lactate-buffered dialysate over 2 48-hour treatment periods in a crossover design.[980] Both solutions effectively raised serum bicarbonate from baseline (bicarbonate group: 18.9 ± 2.0 mmol/l to 22.2 ± 1.2 mmol/l; lactate group: 16.3 ± 1.5 mmol/l to 22.2 ± 1.4 mmol/l). Importantly, serum lactate levels differed significantly; patients dialyzed with lactate-buffered dialysate were found to have higher serum lactate concentrations (mean 2.92 ± 0.45 mmol/l) than those treated with bicarbonate-buffered dialysate (1.61 ± 0.25 mmol/l; $P=0.01$). In participants with hepatic dysfunction, lactate increased to 3.39 ± 0.68 mmol/l in participants randomized to lactate-buffered fluids compared to 1.78 ± 0.42 mmol/l in participants treated with bicarbonate-buffered fluids ($P=0.036$).

The risks associated with bicarbonate-buffered CRRT solutions are minimal when used appropriately and with adequate monitoring. While lactate-based solutions may be more readily available or less expensive in some settings, their use in high-risk populations (e.g., those with shock) may lead to clinically significant metabolic disturbances. Therefore, the balance of evidence and physiological rationale favors bicarbonate-buffered solutions in patients with circulatory shock or liver failure.[608] Implementing bicarbonate-buffered solutions in CRRT requires careful attention to infrastructure, training, and supply chain logistics. These solutions are typically delivered in two-chamber bag systems to prevent calcium-bicarbonate precipitation, necessitating compatible CRRT machines with appropriate software and fluid handling capabilities.

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In low-resource settings, where commercial CRRT solutions may not be readily available, the implementation of bicarbonate-buffered solutions can present additional challenges. Staff must be trained to manage the mixing process and understand the potential implications of incorrect handling. The requirement for two-chamber bag systems or in-house preparation to prevent calcium-bicarbonate precipitation demands appropriate infrastructure, training, and resources that may be limited or competing with other priorities in such environments.[981] Storage requirements are more stringent than for lactate-buffered solutions due to a typically shorter shelf life and temperature sensitivity. Despite these considerations, the widespread adoption of bicarbonate-buffered solutions in commercially available CRRT fluids has facilitated their integration into routine practice.

Bicarbonate-buffered solutions are preferred over lactate-buffered solutions for CRRT in critically ill children and adults with AKI, particularly those with circulatory shock and/or liver failure. This preference is grounded in their superior physiological compatibility and improved safety profile in populations where lactate metabolism is impaired.

Practice Point 5.7.2: CRRT dialysate and replacement solutions should be sterile. Dialysate and replacement solutions for IRRT should comply with American Association of Medical Instrumentation (AAMI) standards regarding contamination with bacteria and endotoxins.

The safety and effectiveness of CRRT are dependent on the composition and quality of dialysate and replacement solutions. In particular, the use of sterile solutions is imperative for CRRT, as these fluids are administered directly into the extracorporeal circuit and may enter the patient's circulation either through convection or diffusion. Contaminated solutions pose a significant risk for bloodstream infections, pyrogenic reactions, and systemic inflammatory responses, which can adversely affect patient outcomes, especially in critically ill populations.

IRRT should at a minimum conform to the AAMI standards for microbial contamination and endotoxin levels. The AAMI standards recommend that dialysate used in hemodialysis contains <200 colony-forming units (CFU)/ml of bacteria and <2 endotoxin units (EU)/ml, with target values of <100 CFU/ml and <0.25 EU/ml for ultrapure dialysate.[982, 983] These thresholds are designed to minimize the risk of chronic inflammation and endotoxin-related complications in patients undergoing dialysis.[982, 983]

In line with the ADQI consensus on precision fluid management in CRRT, the use of biocompatible, sterile, and metabolically favorable fluids is recommended to reduce treatment-related complications and optimize patient outcomes.[984] The combination of sterile delivery and bicarbonate buffering aligns with international best practices and enhances both safety and efficacy in the management of AKI in critically ill populations.

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Practice Point 5.7.3: Locally compounded dialysate and replacement CRRT solutions should be prepared using standard quality control processes or commercially available dialysate and replacement CRRT solutions should be used to allow flexibility in achieving various goals of plasma electrolyte compositions to address most clinical circumstances.

Commercially manufactured CRRT solutions are a preferred option when available, due to their reliable composition, sterility, and regulatory oversight. In clinical settings where commercial CRRT solutions may not be readily available or feasible, locally compounded dialysate and replacement fluids offer a practical and flexible alternative.[981, 985] However, to ensure safety and efficacy, it is essential that such in-house solutions are prepared using standardized protocols, stringent quality control processes, and appropriate staff training.[982, 983]

Several studies support the feasibility and safety of this approach. Yimsangyad *et al.* evaluated the implementation of an in-house, quality-controlled, dialysis solution preparation system for CRRT in a low-resource setting.[985] Over a 12-month period, 48 critically ill patients received a total of 352 CRRT treatments using locally compounded dialysate and replacement fluids.[985] The study found that all prepared solutions met microbial safety standards, with no detectable bacterial contamination or endotoxin levels above acceptable thresholds. Electrolyte concentrations in the in-house solutions remained within ±10% of target values, indicating consistency and reliability in preparation. Importantly, there were no adverse clinical events attributable to the use of these solutions, including catheter-related infections, metabolic disturbances, or hemodynamic instability. From an economic perspective, the in-house production reduced the cost per liter of CRRT solution by approximately 30% compared to commercial alternatives. These findings demonstrate that, when appropriate quality control measures are applied, locally compounded CRRT solutions can be a safe, effective, and cost-efficient option in low-resource healthcare settings.[985] Similarly, Lumlertgul *et al.* described the successful deployment of in-house CRRT solutions during the COVID-19 pandemic, showing that this method could be rapidly scaled in response to supply shortages without compromising patient safety or treatment efficacy.[981]

Practice Point 5.7.4: Base the choice of dialysate and replacement CRRT solutions with specific compositions upon the goals for serum electrolyte and acid–base parameters. The use of dialysate and replacement solutions should be individualized and reassessed at frequent intervals depending upon the clinical condition of the patient to ensure that they are appropriate.

The composition of dialysate and replacement solutions in CRRT should be individualized and routinely reassessed to align with the evolving clinical needs of critically ill children and adults with AKI. Selecting or adapting CRRT solutions with specific

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electrolyte concentrations, such as phosphate-containing, high- or low-sodium, high- or low-potassium, or high-bicarbonate fluids, can support targeted correction of metabolic, electrolyte and acid-base abnormalities.

Phosphate-containing CRRT solutions are increasingly used. Thompson Bastin *et al.* reported that the use of phosphate-containing CRRT solutions was associated with shorter duration of mechanical ventilation and improved phosphate control in adults,[986] while Kim *et al.* showed more stable serum phosphate levels with the use of phosphate-containing dialysate compared with standard solutions.[987]

For patients with disturbances in acid-base balance, especially those receiving RCA, the use of a high bicarbonate-containing CRRT solution may accelerate pH normalization without compromising safety.[988] Additionally, in cases of dysnatremias, adjustments in sodium concentration through customized CRRT solutions may be necessary to achieve gradual and safe correction.[989] Protocols for sodium-based osmotherapy have been developed to guide such individualized management.[990-993] Frequent reassessment, ideally every 6 to 12 hours, is essential given the dynamic clinical course of critical illness and patient susceptibility to rapid shifts in fluid, electrolytes, and acid-base balance.

For patients receiving glucose-free CRRT solutions, vigilance is also required to prevent complications like euglycemic ketoacidosis. In a case series of 8 adults with preexisting diabetes mellitus receiving CRRT with a glucose-free solution, all patients exhibited worsening high-anion-gap ketoacidosis and elevated serum β-hydroxybutyrate levels despite stable or improved lactate levels.[994] The study underscores the importance of monitoring patients for the development of euglycemic ketoacidosis when receiving glucose-free CRRT and highlights the need for proactive nutritional support and glucose supplementation as preventive measures.[994]

Table 53 summarizes the currently available dialysate and replacement CRRT solutions that are available.

Table 53 | Summary of a representative sample of current commercially available dialysate and replacement CRRT solutions

Composition (mmol/l)	Accusol 35	BICSOL 35-108 K0	Prismasol BO	MultiPlus K2	PrismOcal B22	Ci-Ca dialysate	Phoxilium
Na+	140	138	140	140	140	133	140
K+	–	–	–	2	4	2,4	4
CI	109.5	108	109.5	110.5	120.5	116.5	115.9
HCO3	35	35	32	35	22	20	30
Ca2+	1.75	1.5	1.75	1.5	–	–	1.25
Mg2+	0.5	0.75	0.5	0.75	0.75	0.75	0.6

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H2PO4	–	–	–	1.0			1.2
Lactate	–	–	3	-	3	–	–
Glucose	–	5.55	–	5.55	6.1	5.55	–
Citrate	–	–	–	–	–	–	–
Osmolarity	287	289	287	296	296.4	278	293
pH	7.4	7.5	7.0–8.5	7.4	7.0–8.0	7.4	7.0–8.5
Preparation	2-chamber	2-chamber	2-chamber	2-chamber	2-chamber	2-chamber	2-chamber

Ca, calcium; Cl, chlorine; CRRT, continuous renal replacement therapy; H2PO4, dihydrogen phosphate; HCO3, bicarbonate; K, potassium; Mg, magnesium; Na, sodium

5.8. Ultrafiltration in RRT

Practice Point 5.8.1: The target ultrafiltration should be prescribed daily for CRRT and prior to each IRRT session and be frequently monitored.

Fluid accumulation and overload is a common indication for RRT initiation in children and adults.[995, 996] Ultrafiltration, defined as the extracorporeal removal of fluid during RRT, supports fluid management, facilitating resolution of organ edema and weaning from organ support. However, evidence extrapolated from patients with kidney failure receiving maintenance dialysis has shown that rapid ultrafiltration during IHD sessions can induce systemic stress and can precipitate ischemic organ injury (i.e., heart, gut, kidney, and brain).[997-999] Evidence in children and adults implies there is a U-shaped association between the rate of ultrafiltration and mortality.[1000-1003] While an important observation, there are notable limitations to these data, which were derived from retrospective, observational studies or secondary analyses of large RCTs, with inherent challenges to inferences from such data for clinical practice. The primary exposure, rate of ultrafiltration, was generally time-averaged, of variable duration, often dichotomized across these studies.[1000-1005] In addition, the relationship with outcomes is vulnerable to confounding by disease severity.[1006]

The prescription for ultrafiltration should target fluid removal, facilitate weaning from organ support, and not incite harm by worsening or inciting new organ injury.[1000, 1004, 1007] Among critically ill children receiving CRRT, ultrafiltration targeting a negative net fluid balance while also preserving urine output was associated with fewer CRRT-days and lower rates of $MAKE_{30}$.[1008]

This necessitates regular review of the ultrafiltration prescription every 12–24 hours (or more frequently), the net ultrafiltration (UF_{NET}), and patient fluid balance goals.[1009] There is rationale for prescriptions to be weight-based, similar to CRRT dose-intensity (e.g., ml/kg/h) and evidence for UF_{NET} limits in patients receiving IRRT, rather than use of hourly or daily absolute volumes, which may inadvertently expose patients to low or high time-average ultrafiltration and complications from hemodynamic instability or fluid overload.[1010]

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For patients receiving CRRT, healthcare professionals must understand the hourly CRRT device and patient fluid balances.[1011] The CRRT device fluid balance is calculated as the difference in the volume of fluids infused hourly through the CRRT device (e.g., replacement fluids, dialysate solutions, anticoagulant) and the total hourly effluent volume. The patient fluid balance is calculated as the hourly difference in patient inputs (e.g., medications, blood products, nutrition) and outputs (e.g., urine, drains, gastrointestinal), including ultrafiltration. The integration of CRRT device and patient fluid balances are then used to determine the net device-patient fluid balance, which is calculated based on the preceding hour.[984, 1012, 1013] This permits the UF_{NET} rate to be determined hourly and to be aligned with the desired device fluid removal to achieve total fluid balance goals over time (6–24 hours).

Practice Point 5.8.2: The prescribed intensity of ultrafiltration (e.g., timing and rate of removal) should be individualized and consider patient characteristics, clinical context, and phase of illness.

Heterogeneity in patient characteristics, acuity, and evolving phases of acute illness demands that prescribed ultrafiltration be patient- and context-specific and regularly adjusted.[984, 1003, 1014] In children and adults, the optimal prescribed ultrafiltration intensity is uncertain. Existing evidence indicates that the delivery of both low and high ultrafiltration in children and adults may be associated with harm.[1000-1003] As such, the intensity of UF_{NET} should be tailored to patient-specific fluid balance targets while minimizing the risk of adverse events (Table 54). The intensity of UF_{NET} may modify patient outcomes (e.g., mortality; AKI resolution) and should be prescribed to support organ dysfunction resolution while also minimizing harm.[1000, 1001, 1004, 1008, 1015]

Table 54 | Strategies to mitigate adverse events associated with ultrafiltration

Strategy
• Reduce unnecessary fluid administration in critically ill patients to avoid excess accumulation. • Cool dialysate to ≤36ºC. • Prescribe net ultrafiltration (UF_{NET}) by body weight rather than target total volume. • Prescribe a slower UF_{NET} and continuous gradual fluid removal. • Avoid high UF_{NET} while patients are receiving hemodynamic support (i.e., vasopressors). • Review routinely and regularly the UF_{NET} targets and response to fluid removal. • Avoid or minimize prolonged exposure to high UF_{NET} (short-term high UF_{NET} may be indicated and necessary to address life-threatening complications of fluid overload).

Adapted from Murugan *et al*.[1016]

5.9 Discontinuation of RRT

Practice Point 5.9.1: Discontinue RRT when it is no longer needed either because of evidence of resolution of AKI to the point that kidney function is adequate to meet the patient's metabolic and fluid balance demands or because RRT is no longer consistent with the patient's preferences for care.

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Most survivors of acute and critical illness complicated by AKI recover sufficient function to become RRT independent.[713, 815, 1017] Healthcare professionals should aim to frequently and regularly evaluate for indications of AKI resolution, recovery of intrinsic kidney function, and for the potential to feasibly discontinue RRT. This may minimize the duration of risk associated with extracorporeal device/circuit exposure.

The decision on whether to discontinue RRT integrates several considerations, including whether there has been sufficient resolution of AKI and recovery in intrinsic kidney function to meet current demands (e.g., acid-base, electrolyte, azotemic, fluid), whether there has been improvement in the acute illness that precipitated AKI and start of RRT, and whether there is a commitment to ongoing RRT support if a trial of RRT discontinuation is unsuccessful (i.e., change to goals-of-care designation).

Clinical trials have used clinical indications, various metabolic parameters, urine output, and timed creatinine clearance to inform the timing of RRT discontinuation.[820] The Liberation of Acute Dialysis Trial (LIBERATE-D) focused on hospitalized adult patients with AKI who were hemodynamically stable and not requiring vasopressor support.[1018] The trial compared a strategy of continuing IHD for AKI only when specific metabolic or clinical indications were met (e.g., azotemia, hyperkalemia, metabolic acidosis, pulmonary edema, clinical judgement) versus continuing scheduled IHD session 3 times per week until specific urine output (>1 l/d in the absence of diuretics or >2 l/d with diuretics) or creatinine clearance (>20 ml/min) criteria were met.[1018] Among the 221 participants enrolled in the trial, the former strategy resulted in fewer dialysis sessions per week, earlier recovery to IHD independence, and more participants achieving kidney function recovery by the time of hospital discharge.

The strategy to assess for recovery of intrinsic kidney function during RRT depends on the modality being used. For patients receiving IRRT, kidney recovery can be assessed over interdialytic periods, whereas for patients receiving CRRT, relatively steady state can be achieved after 24–48 hour that may enable clearer assessment (e.g., urine volume; urinary excretion of creatinine; timed creatinine clearance, etc.).[1019-1026] However, the current literature is challenging to draw strong inferences from because "successful" RRT discontinuation has been inconsistently defined, ranging from RRT-free between 3–90 days.[1024, 1027] As such, decision-making on RRT discontinuation remains subject to wide practice variation.[1020]

Practice Point 5.9.2: Clinical and metabolic parameters, interdialytic SCr changes, urine output, fluid balance, other parameters of resolution of AKI, and residual kidney function can be used to guide decision-making for RRT discontinuation.

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Interdialytic periods, whether during an interruption in CRRT or between scheduled IRRT sessions, provide an opportunity to evaluate for persistence of clinical and metabolic indications for RRT, as well as signs of AKI resolution and kidney function recovery. In a single center retrospective study, 448 CRRT-free intervals in 222 critically ill adult patients receiving CRRT were evaluated to predict the suitability for a trial of CRRT discontinuation.[1025] Three parameters best predicted successful CRRT liberation: shorter total duration of CRRT, lower Sequential Organ Failure Assessment (SOFA) score, and urine output. Specifically, a higher urine output in the CRRT-free period predicted successful liberation (66 ml/h vs. 10 ml/h).[1025] Similarly, interdialytic periods between IRRT sessions can be used to observe urine output and additional parameters (e.g., timed creatinine clearance).

There have been few clinical risk prediction scores developed to guide decisions for RRT discontinuation.[1025, 1028-1030] In a single center in Korea, 1158 critically ill adult patients receiving CRRT were evaluated for factors associated with successful CRRT discontinuation, defined as being RRT-free ≥7 days after initial discontinuation.[1028] Factors associated with successful CRRT discontinuation were greater urine output (≥300 ml/24h), MAP (50–78 mm Hg), serum potassium <4.1 mmol/l, and BUN <35 mg/dl (serum urea <12.5 mmol/l). A clinical prediction score, comprised of only these 4 variables, had an AUROC 0.73. Another retrospective cohort study in adult patients described the clinical factors predictive of successful CRRT discontinuation, defined as RRT-free survival ≥72 hours after CRRT discontinuation in 1135 critically ill patients with AKI.[1029] Successful discontinuation was observed in 20%. Factors predictive of successful discontinuation included urine output, SCr, cumulative fluid balance, CRRT duration, and receipt of vasoactive therapy. Internal validation showed good discrimination (AUROC: 0.78).

In the LIBERATE-D trial, participants received IHD only when one of the following indications were met: BUN ≥112 mg/dl (serum urea ≥40 mmol/l); hyperkalemia ≥6 mmol/l (>5.5 mmol/l if despite medical treatment); arterial pH <7.15 from metabolic acidosis (or bicarbonate level <12 mEq/l); acute pulmonary edema due to fluid overload responsible for hypoxemia despite diuretic therapy; or clinician judgment.[1018] This strategy increased the likelihood of achieving recovery of kidney function (alive and not receiving dialysis at hospital discharge) compared with continuing treatment 3 times per week until urine output or creatinine clearance criteria were met (64% vs. 50%).

Practice Point 5.9.3: Urine output >450 ml/24 hours without exposure to diuretics or >2300 ml/24 hours with exposure to diuretics and 2-hour timed creatinine clearance ≥23 ml/min can be used to predict successful RRT discontinuation in adults.

While clinical studies have identified various factors associated with successful discontinuation from RRT, most studies have been small and retrospective.[1019-1021, 1023, 1024, 1031, 1032] Urine output has consistently been shown to be an important predictor of successful

RRT discontinuation.[1023, 1024, 1026, 1028, 1031, 1033-1035] All clinical prediction tools developed have integrated urine output as a predictor of successful RRT discontinuation.[1025, 1028-1030] In general, a urine output exceeding >450 ml/24 hours without exposure to diuretics or >2300 ml/24 hours with exposure to diuretics predicts a high probability of a successful trial of RRT discontinuation and serves to guide clinical decision-making.[1020, 1024]

Numerous studies have explored varying urine output thresholds for RRT discontinuation.[1024] In a single center retrospective study of 86 critically ill adults receiving RRT, urine output <0.5 ml/kg/h over 6 hours after CRRT was stopped was associated with lower likelihood of successful liberation (AUROC: 0.91), whereas an urine output of 178 ml/6 hours appears to be the minimum threshold to predict success.[1022] In a retrospective, multicenter study of 213 adults receiving CRRT, greater urine output (>30 ml/h) at the time of discontinuation was the best predictor of success (AUROC: 0.814), defined as CRRT cessation for ≥7 days.[1023]

In adults, the use of a timed creatinine clearance (e.g., 2-hour; 6-hour; 24-hour) can also be used to predict successful RRT discontinuation.[820, 1019] In a small retrospective study, a 2-hour timed creatinine clearance measurement was a reasonable predictor of successful discontinuation, defined as RRT-free at 7-days, when performed in the 12-hours prior to CRRT discontinuation.[1019] A threshold 2-hour creatinine clearance of 23 ml/min was associated with a sensitivity, specificity and positive predictive value for successful discontinuation of 75.5%, 84.4%, and 88.8%, respectively.

Practice Point 5.9.4: Use of diuretic therapy prior to and following RRT discontinuation can be used to augment urine output and manage fluid balance but has not been proven to facilitate resolution of AKI.

The use of diuretics, predominantly furosemide, is common among patients with AKI.[1036] Large cohort studies have shown up to two-thirds of critically ill adults with AKI are exposed to diuretic therapy.[1037] In the Standard versus Accelerated Initiation of Renal Replacement Therapy in Acute Kidney Injury (STARRT-AKI) trial, diuretic exposure prior to randomization occurred in 35% of participants.[713] In the Initiation of Dialysis Early Versus Delayed in the Intensive Care Unit (IDEAL-ICU) study, diuretic exposure exceeded 50% in the 7 days following enrollment[124], whereas in the AKIKI trial, 18.7% were exposed to diuretic therapy prior to starting RRT, predominantly in the delayed RRT strategy compared with the early strategy (36.5% vs. 1.3%, p<0.001).[712]

The use of diuretics is also common among critically ill children prior to and after CRRT initiation.[1038] In a large European survey of pediatric ICU practice, 39% reported using diuretic therapy during CRRT and up to one-third reported using a diuretic challenge, either as a bolus alone or followed by a diuretic infusion during CRRT discontinuation.[891]

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Diuretic therapy in patients with AKI is most often used to facilitate urine output and prevent or treat complications of fluid accumulation.[433, 1037] Evidence indicates that exposure to diuretics alters the urine output threshold for predicting successful RRT liberation.[1020, 1022] A robust urine output response to a diuretic challenge may provide added information on the likelihood of successful RRT discontinuation.[1022, 1031, 1033] Importantly, there is no compelling evidence to suggest that the pre-emptive use of diuretics can facilitate more rapid resolution of AKI;[1039, 1040] however, diuretics have an adjuvant role in augmenting urine output and for managing fluid balance upon RRT discontinuation. In a small single center RCT, a continuous infusion of furosemide after RRT discontinuation was associated with augmentation of urine output and natriuresis but there was no difference in rate of AKI resolution or RRT independence.[1041]

5.10 Quality assurance for RRT

Practice Point 5.10.1: RRT programs should include the following quality standards to reduce unnecessary variation, facilitate adoption of evidence-based practices, and support opportunities for continuous quality improvement:

- **Dedicated leadership, ideally with a medical (physician) and nursing dyad partnership.**
- **Certified training and continuous education of all healthcare professionals prescribing and delivering acute RRT.**
- **Standardized order sets for the acute prescription of RRT, including decision-support for dose-intensity of solute clearance, ultrafiltration for fluid removal, and anticoagulation strategy.**
- **Standardized charting for RRT for both conventional and electronic health records, inclusive of parameters of patient and machine solute clearance and fluid balance.**
- **Monitoring and reporting of quality and key performance measures of RRT**

Variations in standards of practice for how RRT is prescribed, monitored, and delivered[829] can stem from differences in operational organization (e.g., nephrology, intensive care, or both), knowledge gaps, and suboptimal implementation of evidence-based practices.[1012, 1013, 1042] The integration of quality standards and routine indicators of performance specific to acute RRT can reduce unnecessary variation and harmonize practice, improve adoption of evidence-based practices, and identify opportunities for iterative continuous quality improvement.[791, 1012, 1043]

Acute RRT programs can more effectively drive quality and innovation with dedicated leadership.[831-833, 1044] This construct is supported by numerous organizations and societies.[708, 788, 790, 791, 1045] Local leadership and championing of quality initiatives in acute RRT is foundational to building a team and creating a culture of continuous quality improvement and innovation.[790, 1046]

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RRT programs are highly specialized and depend on a multidisciplinary team (e.g., physician, nurse, dietician, pharmacist, biomedical engineer, medical informatics) that is specifically trained to prescribe, deliver, and monitor acute RRT.[1042] Education is fundamental to enable practice standardization and delivery of high quality RRT. A modified Delphi process identified education and training as a high priority for acute RRT programs; however, it was recognized that the specialized training for RRT, particularly CRRT, was poorly described and characterized.[1042] This is likely to contribute to disparities in practice across institutions. The *Saving Young Lives* program identified the importance of "hands-on" training and successfully empowered clinical teams to deliver standardized acute PD for AKI in low-resource settings.[790]

The use of standardized order sets with integrated decision-support, including integration of current literature and guideline recommendations, can facilitate greater practice harmonization and alignment with delivery of evidence-based RRT standards.[791, 834] The growing utilization of EHR can be leveraged to provide a platform for consistent charting and sharing of performance indicators, including the development of local benchmarks and detection of avoidable deviations in practice.[743, 1043] The EHR can be an important tool for identifying evidence-to-care gaps and for the implementation of continuous quality improvement.[1047]

Practice Point 5.10.2: Key quality performance measures of RRT include measures of effective treatment time (i.e., downtime), filter lifespan, prescribed-to-delivered dose-intensity, and ultrafiltration.

There has been limited development and validation of key quality and performance indicators for RRT for AKI despite its resource implications.[1013, 1043] A modified Delphi study developed a prioritized list of CRRT quality indicators from an international interdisciplinary panel of experts (Table 55).[1042]

Several studies have described specific indicators of acute RRT performance, mostly among patients receiving CRRT which focused on filter lifespan, effective treatment time, and delivered dose-intensity.[829, 831-833, 1013, 1044] Effective treatment time, defined as the measured time receiving treatment minus any interruptions, either planned or unplanned, has been proposed as a quality indicator of CRRT performance.[834] This quality indictor is focused on describing total CRRT treatment downtime in a 24-hour period. While interruptions may be unavoidable, it is important to recognize that downtime can compromise the effectiveness of therapy and result in discrepancy between the prescribed and actual delivered therapy.[815, 820, 839, 856-861]

A multifaceted quality improvement initiative significantly improved effective treatment time by focusing on minimizing avoidable downtime.[1044] Another single center quality improvement study that leveraged a local EHR showed marked improvement in

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CRRT dose-intensity standardization and reduced week-to-week variation.[832] Similarly, a staged multifaceted quality improvement project that included the development of a multidisciplinary team, use of a standardized CRRT protocol, implementation of quality measures, and an educational initiative was shown to substantially improve delivered CRRT dose-intensity, prolong filter lifespan, reduce CRRT access alarms, and realize meaningful cost savings.[833] These initiatives profile the importance of having key performance and quality indicators that measure baseline practice and gauge iterative improvement over time (Table 55).

Table 55 | Key quality/performance measures of CRRT[1042]

CRRT key performance indications	Operational definition	Proposed benchmarks*
CRRT leadership	Dedicated CRRT physician/nurse dyad	100%
CRRT education	Proportion of CRRT providers with certified training	>90%
Filter life	Proportion of unplanned filter exchanges	<50%
Downtime (daily)	24 hours - CRRT run-time/24 hours	<15%
Access alarms	Number of access alarms/day	<3
Dose-intensity	Median prescribed dose-intensity Proportion of treatments delivered at recommended dose (20-25 ml/kg/h)	20-25 ml/kg/h >85%
Ultrafiltration	Delivered/prescribed ultrafiltration	>85%
Adverse events	Counts and rates of significant adverse events	<1 per CRRT-day/week
RRT discontinuation	RRT liberation (RRT independent)	>75%
ICU mortality	Patient survival to ICU discharge (%)	>50%

*Benchmarks are proposed and should be individualized by acute RRT programs. CRRT, continuous renal replacement therapy; ICU, intensive care unit; RRT, renal replacement therapy

5.11 RRT with extracorporeal life support (ECLS)

Practice Point 5.11.1: Strategies for integration of RRT into existing circuits in patients receiving extracorporeal life support (ECLS) depend on clinical context, local expertise, and available technology and resources.

ECLS (e.g., extracorporeal membrane oxygenation [ECMO], extracorporeal carbon dioxide removal [ECCO$_2$R], and ventricular assist devices [VAD]) is a long-established cardiopulmonary life support therapy used to manage patients with life-threatening refractory cardiogenic shock or acute respiratory failure.[1048-1051] It is associated with a high risk for AKI, in both children and adults.[1052-1054] Up to 40% of children and 30% of adults receiving ECLS concomitantly receive RRT.[1053, 1055, 1056] CRRT is the predominant modality used

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during ECLS in both children and adults.[1057, 1058] The most common indication for RRT during ECLS is fluid accumulation and fluid overload that is refractory to or is perceived to be inadequately managed by medical therapy.[1057, 1059, 1060]

There are techniques to introduce RRT for patients also receiving ECLS.[1059, 1061-1063] These generally include: 1) dedicated and independent RRT access and circuit (parallel); 2) integration of a hemofilter directly into the ECLS circuit (in-line hemofilter); 3) integration of a full CRRT device/circuit into the ECLS circuit (series).

RRT can be provided through a conventional dedicated dialysis catheter in a separate central vein that will run in parallel with the ECLS circuit.[1059, 1062, 1063] This configuration has the advantages of RRT being operated and delivered in a standard manner, not having issues with differential access pressures when combined with the ECLS circuit and the option of prescribing/delivering solute clearance and ultrafiltration as per standard protocols and procedures. This technique can allow the dedicated use of standard anticoagulation (e.g., RCA). Moreover, there should be no concern for the ECLS circuit if the CRRT circuit requires interruption or change. A downside is the need for separate vascular access.

Alternatively, RRT can be integrated into the ECLS circuit through a variety of techniques. A simple and relatively inexpensive method is the direct introduction (in-line) of the hemofilter into the ECLS circuit.[1057, 1060] For the in-line configuration, the hemofilter is typically integrated after the ECLS blood pump to provide positive pressure into the hemofilter and before blood flow enters the membrane lung (oxygenator). (Figure 18) This technique will require minimal expansion of the extracorporeal blood volume; however, it can present challenges with monitoring (e.g., no access pressure alarms), external infusion pumps are necessary to deliver replacement solutions, and it may not enable precision control of ultrafiltration.[1059, 1062-1064]

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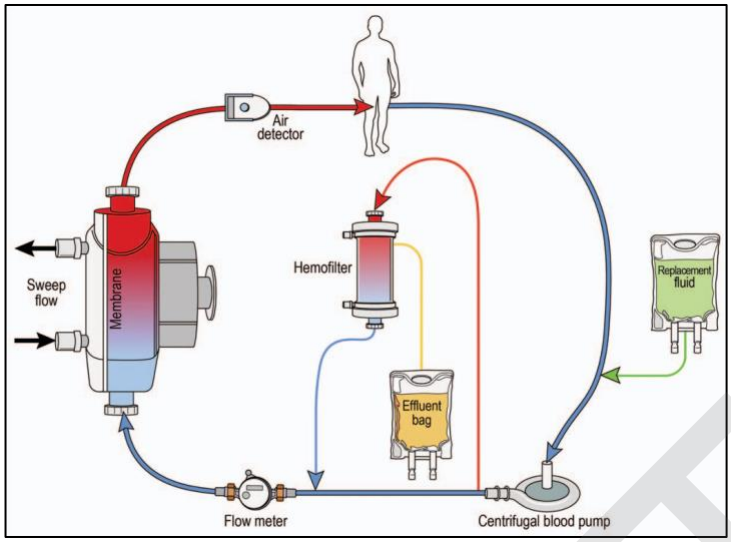

Figure 18 | Configuration of in-line hemofilter integration into ECLS circuit.[1062] ECLS, extracorporeal life support

Another option is the integration of a commercially available CRRT device into the ECLS circuit.[1059, 1062, 1063] This configuration will enable superior control of dose-intensity and ultrafiltration compared to an in-line configuration. A drawback of this technique relates to the challenges with CRRT access pressures.[1065-1067] ECLS circuit pressures are negative before the blood pump and positive between blood pump and membrane lung.[1059] These pressures can exceed the operational limits for CRRT devices and may contribute to frequent pressure alarms and potential complications in both circuits. As aforementioned, to prevent systemic embolization of air/clots, the CRRT should be integrated after the ECLS blood pump and before the membrane lung.[1059]

Finally, it is also possible to connect the CRRT circuit using the existing inlet and outlet Luer locks in the membrane lung (Figure 19).[1062, 1063, 1067] This configuration will circumvent the access pressure issues and enable delivery of dose-intensity and ultrafiltration.

Combined ECMO-RRT support necessitates expertise, protocols and standardized procedures to ensure all CRRT venous and arterial accesses are maintained in the correct pressure ranges and do not disrupt the ECLS circuit.[1059, 1065, 1066]

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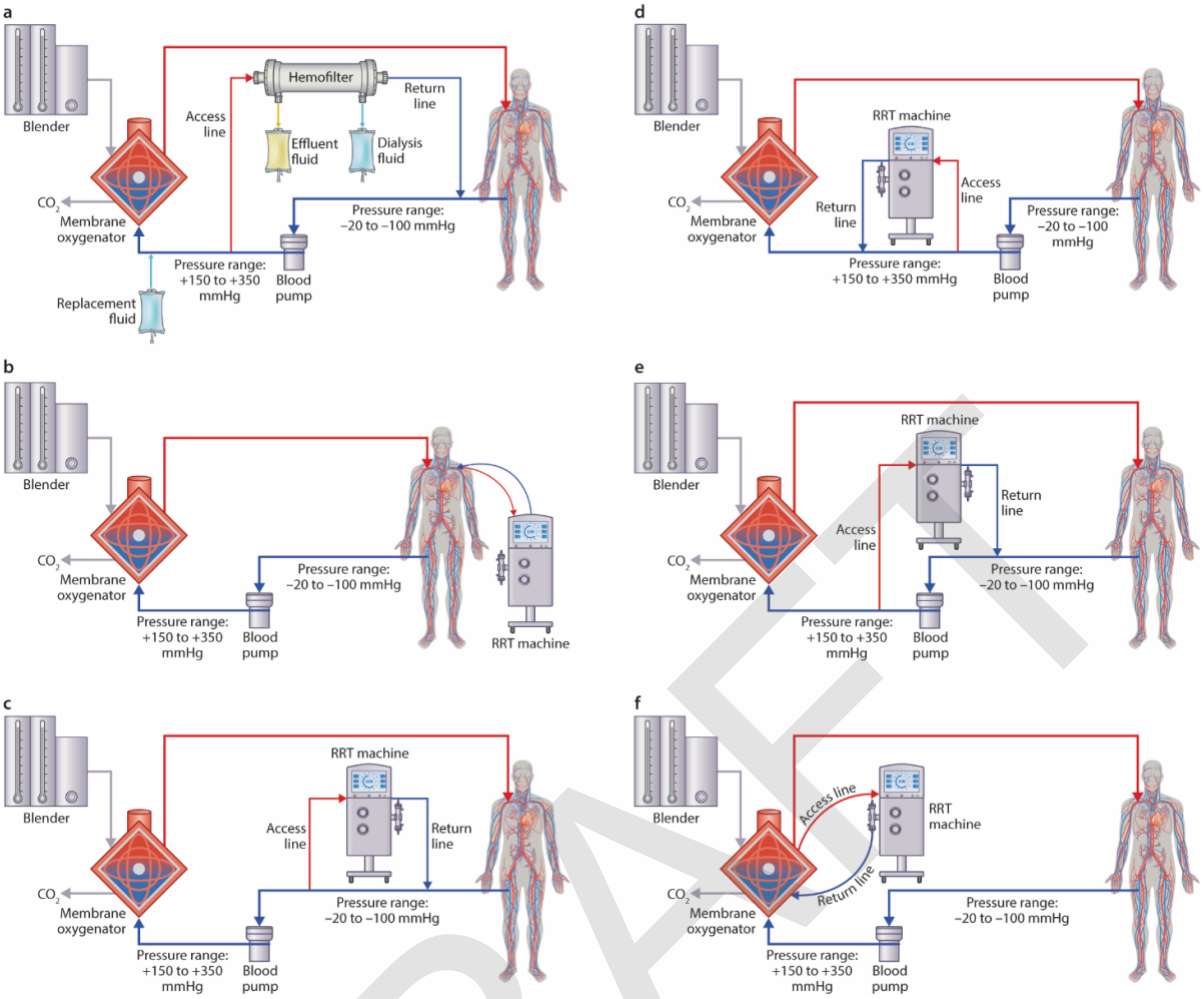

Figure 19 | Options of combining ECMO and CRRT circuits.[1068] a. An in-line hemofilter is integrated into the ECMO circuit. Replacement fluid is directly administered into the ECMO circuit. Alternatively, dialysis fluid can be supplied in a counter-current position. Replacement/dialysis fluid rates and ultrafiltration rates can be controlled via infusion pumps. b. The CRRT device is connected to the patient through a separate catheter independent of the ECMO circuit. c. The access (inlet) and the return (outlet) lines of the CRRT device are connected before the centrifugal blood pump (low-pressure part) of the ECMO circuit. d. Both the access and the return lines of the CRRT device are connected after the blood pump. e. The access line of the CRRT device is connected after the blood pump (high-pressure), while the CRRT return line is connected before the centrifugal blood pump. f. The access line of the CRRT device is connected directly after the membrane oxygenator, while the return line is connected directly before the oxygenator. CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation.

All configurations have potential serious risks, including air embolism, hemolysis, and formation of blood clots. There is no clear evidence that any specific configuration is superior in terms of outcomes or safety. However, if a centrifugal pump is used, it is preferable to connect the CRRT device after the pump because of the risk of drawing air into the ECMO circuit. The Extracorporeal Life Support Organization (ELSO) have published guidelines on the management of AKI and fluid overload during ECLS, along with technical

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guidance and considerations for RRT.[1059] The decision on the precise configuration of RRT and ECLS should be guided by local expertise, experience and the implementation of standardized protocols and procedures.

Practice Point 5.11.2: Most patients receiving ECLS have concomitant hemodynamic instability. For these patients, initial support with CRRT rather than IRRT may be preferential.

Survey and observational data show that most ECLS patients with AKI who need RRT receive CRRT.[1057, 1060, 1069] The rationale for CRRT is driven by most ECLS patients having high illness acuity, hemodynamic instability, and multiorgan dysfunction.[1048, 1055, 1056, 1061] Fluid accumulation and overload is the primary trigger for RRT in most patients receiving ECLS.[1057, 1059, 1060] While all modalities of RRT can be delivered during ECLS, these critically ill patients are less likely to tolerate the more rapid shifts in metabolic profile and faster ultrafiltration that will occur with IRRT. CRRT has the advantage of enabling consistent and continuous fluid removal with reduced risk of fluctuations that may disrupt the ECLS blood flow.

Practice Point 5.11.3: Fluid accumulation that is refractory to medical therapy independent of kidney function may be a reasonable indication for RRT in patients receiving ECLS.

Fluid accumulation and overload with and without AKI is associated with worse clinical outcomes, including mortality and longer durations of organ support and ICU stay.[432, 1014, 1070-1073] While regimens of diuretic therapy can be used to manage fluid, individual response in patients can be inconsistent and insufficient to meet fluid balance targets. Medically refractory fluid accumulation is a reasonable indications for starting RRT.[1059, 1074-1076] Fluid accumulation and overload are recognized indication for RRT initiation among critically ill children receiving ECLS.[1057, 1060] In these patients, achieving a negative fluid balance can be associated with improved oxygenation.[1077]

5.12. Considerations specific for children

5.12.1 Starting renal replacement therapy (RRT)

Practice Point 5.12.1.1: In critically ill children with severe AKI, RRT initiation within 2 days of intensive care unit (ICU) admission or AKI onset should be considered as it may be associated with improved outcome.

AKI is a recognized risk factor among children for escalation in care intensity (e.g., mechanical ventilation; RRT) and adverse outcomes, including mortality and long-term health complications (e.g., neurocognitive and functional impairment, hypertension, CKD).[1017, 1078-1087] Randomized trials investigating early versus standard/delayed initiation of RRT have only been performed in adults. However, the increased risks of catheter and therapy-specific risks of RRT with early RRT initiation

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observed in RCTs of adults are likely generalizable to children. RRT initiation translates into an escalation in care intensity, complexity, and costs. For acutely and critically ill children with persistent severe AKI and/or fluid overload, these burdens of starting RRT may be balanced by reductions in durations of invasive organ support (i.e., mechanical ventilation; ECLS) or lengths of ICU or hospital stay. Durations >48 hours after ICU admission or AKI onset to the start of RRT among critically ill children with AKI have shown an association with $MAKE_{90}$.[732, 1088, 1089]

In low- and middle-resource settings, the capacity for and options to provide acute RRT may be reduced, including limited access to critical care services and/or selected acute RRT modalities. A "PD first" approach has been successful in pediatric centers in low- and middle-resource settings with locally produced PD fluids and repurposing of different catheters.[789, 1090]

The timing and indications for starting RRT among children, particularly among those with critical illness and persistent severe AKI warrant further evaluation.[1089, 1091] Among selected case-mix (e.g., complex congenital cardiac surgery) and circumstances (e.g., ECLS), decision-making may be driven by rapid evolution in clinical status, acuity, perceived complications compounded by AKI, and need for concomitant therapeutic support (e.g., ability to provide adequate nutrition[1092, 1093]), justifying earlier start to RRT or initiation in the absence of conventional indications or AKI and related complications that were evaluated in RCTs focused on critically ill adults with AKI. Adoption and implementation of these practice points should be further studied and be guided by process-based quality assurance.[831]

Practice Point 5.12.1.2: In critically ill children, isolated fluid overload can be an indication for RRT initiation.

Fluid accumulation and overload in children with and without AKI are associated with adverse outcomes and greater health resource use (e.g., prolongation of mechanical ventilation; longer lengths of stay).[432, 1094-1096] Children with AKI commonly accumulate fluid, and many, though not all, have coexisting fluid overload.[1097]

A proposed definition of fluid overload is the presence of "a pathologic state of positive fluid balance associated with a clinically observable event(s), which may vary by age, case-mix, acuity, and phase of illness".[1098] While there may be no universal threshold of fluid balance to define fluid overload across all acute and critically ill children or for use as a trigger for RRT initiation[1094, 1099], adverse outcomes associated with fluid overload (with or without AKI), prolonged oligo-anuria, and the need for precise fluid management are frequent indications for starting RRT in acute and critically ill children.[1091, 1099, 1100] Based on observational studies in children, fluid overload is considered an important indication for RRT initiation that has been associated with clinical outcomes. There remains uncertainty about whether RRT and the relative timing of initiation of RRT can modify the risks of adverse outcomes associated with AKI and/or fluid overload in children.[166]

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The strategy of early PD initiation to prevent fluid overload among high-risk children undergoing cardiac surgery has shown variable results for time to achieve target fluid balance, durations of mechanical ventilation, and ICU length of stay, risk of adverse events, and mortality when compared to conservative management, including the use of diuretic therapy.[1101-1106]

5.12.2. RRT modality

Practice Point 5.12.2.1: Acute PD is an acceptable RRT modality and may be preferable to CRRT for children in select circumstances.

There have been limited direct comparisons of RRT modalities for AKI in children;[1107, 1108] however, secular trends have shown greater utilization of CRRT and IRRT over time, with reductions in use of acute PD, [1109] likely in part related to the introduction of miniaturized devices aimed to provide RRT in acute and critically ill children (Table 56).[1110-1113] However, PD is an acceptable RRT modality for selected children with AKI or with complications of fluid accumulation, in low- and middle-resource settings, and in circumstances when extracorporeal RRT is contraindicated or not possible. In pediatric AKI, acute PD is often favored due to the smaller blood volumes and lower tolerance for rapid hemodynamic changes in children. Additionally, peritoneal access via a catheter does not require anticoagulation and is vessel sparing, avoiding catheter associated thrombi commonly seen in younger children. There has been only one small single-center RCT comparing acute continuous PD to daily IHD among 136 critically ill children (age 1 month to 16 years) with AKI.[1108] While azotemic control and rates of complications were similar between the groups, children allocated to acute PD had significantly higher survival at 30 days compared to children receiving IHD (60.7% vs. 36.5%, P=0.019). Among those allocated to IHD, death was most often associated with cardiac failure, sepsis, hypotension, and disequilibrium syndrome. The remaining literature on acute PD in children has focused specifically on the population undergoing cardiac surgery and most often compares either PD catheter placement alone with or without acute PD versus conservative (non-RRT) measures, such as the use of furosemide, to manage perioperative fluid balance.[1101-1105, 1114]

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Table 56 | Summary of parameters for RRT modalities in critically ill children

	IHD	SCUF	CVVH	CVVHD	CVVHDF	PD
Q_B (ml/kg/min)	5–8	3–5	3–5	3–5	3–5	N/A
Mechanism for solute transport	Diffusion*	Convection	Convection	Diffusion	Diffusion & convection	Diffusion
UF_{NET} (ml/kg/h)	0–2.5	0–2.5	0–2.5	0–2.5	0–2.5	Variable
Q_D (ml/kg/h)	Individualized sometimes exceeding Q_D/Q_B >2:1 to maximize urea clearance	N/A	N/A	20–30	20–30	8–20 ml/kg or 800–1100 ml/m^2 per exchange
Q_R (ml/kg/h)	Variable	N/A	20–30	0	20–30	0

*Diffusion ± convection when used with hemodiafiltration. CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; IHD, intermittent hemodialysis; N/A, not applicable; PD, peritoneal dialysis; Q_B, blood flow rate; Q_D, dialysis flow rate; Q_R, replacement fluid rate; RRT, renal replacement therapy; SCUF, slow continuous ultrafiltration; UF_{NET}, net ultrafiltration

5.12.3. RRT dose-intensity

Practice Point 5.12.3.1: An initial CRRT effluent volume for children can be 25–30 ml/kg/h. Thereafter, dose-intensity can be adjusted based on the adequacy of correction of electrolyte, acid-base, and metabolic derangements.

There are no RCTs to support a target RRT dose-intensity for acutely ill or critically ill children. Due to limited comparisons of outcomes according to delivered RRT dose-intensity in children, this practice has generally been extrapolated from findings of RCTs performed in adult populations.[815, 820]

Practice Point 5.12.3.2: The dose-intensity prescription in children receiving CRRT should be weight-based (ml/kg/h), according to either body weight at hospital or ICU admission or ideal body weight and not prescribed based on body surface area.

The optimal initial RRT dose-intensity in children is unknown. Survey data have shown variation in practice, with both weight-based and body surface area (BSA)-based methods commonly used.[938, 1091] Importantly, the relationship between body weight and BSA in children is nonlinear, presenting challenges in translating and aligning prescribed dose-intensity between these methods, driven by large differences in age, body weight, and body morphology across the spectrum of children encountered. For example, in neonates and infants, an initial CRRT dose-intensity based on BSA of 2 l/h per 1.73 m^2, common in survey

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data, could translate to an unintended much higher weight-based CRRT dose-intensity of 70–100 ml/kg/h.[1091] This reinforces the necessity for routine and frequent monitoring of CRRT (Practice Point 5.3.2 and Practice Point 5.12.3.1). Moreover, body weight at the time CRRT is initiated may be confounded and unreliable due to acute illness and fluid accumulation, implying body weight at hospital or ICU admission, or ideal body weight be preferentially used.

Practice Point 5.12.3.3: In children with AKI, PD can be initiated with a fill volume of 10–20 ml/kg and short cycle times (60–90 minutes), with gradual increases in volume and dwell time as tolerated, with continuous therapy over 24 hours for the first 1–3 days to achieve solute clearance and fluid balance goals.

The issue of prescribing and achieving adequate clearance using acute PD in children with AKI was specifically addressed in the 2020 updated ISPD Guideline for PD in AKI (Pediatric).[776] This practice point aligns with this guideline. Age is an important determinant of RRT modality selection in critically ill children, with many children under age 6 years receiving acute PD.[776] Acute PD can generally provide sufficient metabolic, azotemic and volume control for most children, including those who are hypercatabolic.[1115] Initial fill volumes of 10–20 ml/kg are recommended to reduce the risk of dialysate leakage.[1116] Thereafter, fill volume can be slowly increased to optimize solute clearance and ultrafiltration. While initial dwell and drain times should be every 60–90 minutes, in extreme and very-low birth weight infants, lower fill volumes (7–14 ml) and shorter dwell times (10–20 minutes) may be necessary.[1117]

Practice Point 5.12.3.4: Augmentation of initial RRT dose-intensity for CRRT is warranted when treating children with hyperammonemia. CRRT dose-intensity up to 200 ml/kg/h may be acceptable to achieve adequate clearance of ammonia. Children should be appropriately monitored for unintended solute losses during periods of augmented CRRT dose-intensity.

Ammonia can be generated in excess due to inborn errors of metabolism, poisoning, sepsis, or acute liver failure. Ammonia is a neurotoxin and accumulation can precipitate metabolic encephalopathy, cerebral edema, or death.[1118, 1119] Serum ammonia concentrations >100 μmol/l reliably predict severe encephalopathy among patients with acute liver failure.[1120] As such, hyperammonemia is a recognized indication for RRT.[754, 1091, 1121-1128] IRRT can efficiently clear ammonia and is dependent on blood flow rate, dialysate flow rate, and hemofilter surface characteristics; however, use of short-term IRRT sessions may result in rebound elevation in serum ammonia.[1127, 1129, 1130] Extracorporeal clearance of ammonia using initial high dose-intensity CRRT (total effluent flow >75–90 ml/kg/h) has shown capacity to achieve 50% reduction in serum ammonia concentrations within 4–9 hours.[1119, 1127, 1131, 1132] A biphasic CRRT dose-intensity strategy may mitigate the risk of cerebral edema.[1118] CRRT (CVVHDF) has been recommended for children with serum ammonia

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>400–500 µmol/l and not responsive after 4 hours of aggressive medical therapy (e.g., protein restriction; ammonia chelation).[1127, 1133]

5.12.4. Catheters for RRT

Practice Point 5.12.4.1: In small children, including neonates with small vessel size, use of a pliable cuffed catheter, as compared to a rigid temporary catheter, may be less thrombogenic and preferred, even when the expected dialysis duration is uncertain. The cuff can be left outside the body when the projected duration of use is short.

In neonates and small children requiring RRT for AKI, vascular access poses significant challenges due to the small caliber of blood vessels, limited available access sites, and a heightened risk of access-related complications. In this context, the use of a soft, pliable, cuffed catheter, rather than a rigid, temporary catheter, may provide superior safety and performance, even when the anticipated duration of RRT is uncertain. Rigid nontunneled catheters, which are commonly used in adults, may be less appropriate for small children because of an increased risk of mechanical trauma to fragile vessels, higher thrombogenicity in low-flow states, and limited flexibility that can lead to malposition or kinking.[913, 1134]

In contrast, pliable cuffed catheters made of softer materials such as silicone or polyurethane are associated with reduced endothelial injury and a lower risk of thrombosis, improved catheter patency in small vessels, and greater flexibility and comfort, all of which help to minimize mechanical complications.[1134] Although these catheters are typically designed for long-term use, they may still offer advantages in short-term settings for neonates and infants, especially in cases where vessel preservation is a priority. When short-term use is anticipated, the catheter cuff can be left external to the skin to avoid subcutaneous tunneling and to facilitate easier removal.[1135] Additionally, cuffed catheters offer improved securement and stability, which is especially important in infants and young children who are more prone to accidental dislodgement.

5.12.5. Anticoagulation for RRT

Practice Point 5.12.5.1: In children requiring small catheters and circuit volume and lower blood flow rates, anticoagulation is often necessary and preferred over no anticoagulation during CRRT.

In critically ill children receiving CRRT, the use of anticoagulation is often necessary due to the unique technical challenges posed by smaller catheter sizes, reduced extracorporeal circuit volumes, and lower blood flow rates. These factors contribute to an increased risk of circuit clotting and premature filter failure in the absence of anticoagulation.[1136, 1137] Data from a multicenter European observational cohort study including 247 children undergoing CRRT with 1357 circuits totaling 37,562 treatment hours (EurAKID registry) demonstrated that shorter circuit lifespan in children is influenced by

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reduced circuit size and flow dynamics, both of which are more prone to clotting without adequate anticoagulant support.[1137]

Brophy *et al.* conducted a multicenter evaluation highlighting how anticoagulation, particularly RCA or UFH, used during CRRT significantly improved filter lifespan and reduced clotting events compared to circuits managed without anticoagulation.[1136] Further, in a study of 161 children receiving CRRT (total 22,190 hours; median 74.8 hours per patient), filter lifespan was significantly shorter for CRRT without anticoagulation, especially in younger children and those with lower blood flow settings.[1138]

5.12.6. Hemofilters for RRT

Practice Point 5.12.6.1: Appropriately sized membranes proportional to body surface area are preferred for children with AKI receiving CRRT or IRRT.

In children with AKI receiving CRRT or IRRT, selecting a filter membrane with a surface area proportionate to the child's body surface area is essential to ensure both treatment efficacy and safety. Children, particularly neonates and infants, have lower circulating blood volumes and limited tolerance for extracorporeal circuits. Oversized membranes can significantly increase extracorporeal volume, raising the risk of hemodynamic instability, hypothermia, and the need for blood priming.[1139]

Coulthard and Sharp examined the feasibility and challenges of hemodialysis in very small infants, including those weighing as little as 2.5 kg. They described the use of extracorporeal circuits with a volume of approximately 25 ml.[1139] Given that the estimated total blood volume in infants is around 80 ml/kg, a 2.5 kg infant would have a total blood volume of about 200 ml. Thus, the extracorporeal volume represents approximately 12.5% of the infant's total blood volume. This relatively high proportion poses significant risk for hemodynamic instability and necessitates the use of blood priming.[1139]

Using an oversized membrane can lead to an increase in extracorporeal circuit volume, which may exceed 8–10 ml/kg and increase the risk of hemodynamic instability, particularly in neonates and small children.[1140] Additionally, large membranes, even with blood priming, can cause dilutional coagulopathy, with reductions in platelet and fibrinogen levels due to large extracorporeal volumes. Larger membranes are also associated with higher RRT-related macro- and micronutrient losses.[1141, 1142]

Conversely, undersized membranes may compromise RRT adequacy. Therefore, proportional membrane sizing is a critical component of safe and effective CRRT delivery in pediatric patients.[1091] In the EurAKID registry, longer hemofilter lifespan was associated with use of RCA (42 h for RCA vs. 24 h for UFH versus 18 h for no anticoagulant, P=0.001), larger membrane surface area, and right internal jugular access (compared with left internal jugular).[1137] Notably, smaller dialyzers (membrane surface area <0.5 m^2) had shorter

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lifespans (19 h; IQR: 14–32) than both medium (membrane surface area 0.5–1.0 m^2–26 h; IQR: 16–43, *P*=0.04) and large dialyzers (membrane surface area >1.0 m^2–33 h; IQR: 20–48, *P*<0.001).[1137]

Pediatric-specific CRRT machines and miniaturized circuits are available and have received regulatory approval. In the absence of direct comparative pediatric studies, selection of CRRT platforms should prioritize overall biocompatibility, low extracorporeal circuit volume, and suitability for patient size. When available, hemofilters with validated safety data in small children are preferred.[1107, 1110, 1112, 1143] If higher solute clearance is required, membrane surface area may be increased as clinically indicated. Importantly, the advantages of pediatric-specific CRRT platforms extend beyond filter size alone. Appropriately scaled machines are designed to allow precise and reliable fluid balance control, which is particularly critical in neonates and small children, where even minimal fluid deviations may be clinically significant. In addition, these systems support lower blood flow rates, which may reduce shear stress, limit blood–surface interaction and potentially decrease the risk of hemolysis and inflammation. Together, these features may enhance the safety, feasibility, and tolerability of CRRT in small pediatric patients and should be considered when selecting CRRT technology for this population.

5.12.7. Ultrafiltration in RRT

Practice Point 5.12.7.1: In children, net ultrafiltration (UF_{NET}) should not exceed 2.5 ml/kg/h. Frequent assessment of fluid balance (i.e., every 4-6 hours) should be undertaken to evaluate tolerance for fluid removal and adjust fluid balance goals, as necessary.

Fluid overload is a frequent indication for CRRT initiation in critically ill children and associated with adverse outcomes.[996, 1009, 1071, 1075, 1076] Limited data in critically ill children with AKI, particularly among those with fluid overload >20% of body weight, suggest early net negative fluid balance after CRRT initiation may modify outcome.[996] Similar to adults, there is concern that high UF_{NET} in children may contribute to dialysis-induced kidney injury and be associated with adverse outcomes.[1008] Thadani *et al*. evaluated the association of net fluid balance after CRRT initiation in 371 critically ill children, mostly with AKI.[1008] Those who achieved a net negative fluid balance had more CRRT-free days and lower risk of $MAKE_{30}$. Moreover, children maintaining urine output ≥0.3 ml/kg/h over the study period were found to have 5.6 more CRRT-free days and a decreased rate of MAKE. Preservation of urine output has been shown as a potentially important indicator of UF_{NET} intensity and associated with CRRT liberation.[1144]

An upper UF_{NET} threshold <2.5 ml/kg/h has been suggested to minimize the risk of adverse events attributable to ultrafiltration and facilitate safe fluid removal among critically ill children. Frequent assessment and adjustment of UF_{NET} and fluid balance targets among critically ill children are essential to mitigate risk of harm.

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5.12.8. Discontinuation of RRT

Practice Point 5.12.8.1: Urine output exceeding >0.5 ml/kg/h over 6 hours can indicate resolution of AKI and be used to predict successful RRT discontinuation in children.

Critically ill children receiving CRRT are characterized by a high burden of multiorgan dysfunction, beyond AKI and fluid overload.[758] Surveillance of practice has suggested the most important factors used by healthcare professionals when deciding to discontinue CRRT among critically ill children are urine output and resolution of fluid overload.[891] Relatively few studies have focused on factors predictive of successful RRT discontinuation. An analysis of the multinational WE-ROCK study evaluated predictors of successful CRRT discontinuation, defined as no reinitiation of RRT for ≥72 hours in 622 critically ill children.[1144] In this large cohort, only 54% of children successfully discontinued CRRT. Several factors were associated with successful CRRT discontinuation, including variables prior to CRRT initiation (higher urine output), variables at the time of CRRT initiation (higher Vasoactive-Inotropic Score; higher Pediatric Logistic Organ Dysfunction-2 score) and a shorter total CRRT duration.

In addition, a single-center retrospective study reinforced the prognostic value of urine output when predicting successful CRRT discontinuation in children. In a cohort of 99 critically ill children who underwent a trial off CRRT, urine output ≥0.5 ml/kg/h in the 6 hours prior to stopping CRRT predicted successful discontinuation (AUC: 0.72, 95% CI: 0.60–0.84, *P*=0.0009), defined as no reinitiation of CRRT for ≥7 days.[1145] Notably, this association remained significant after adjustment for diuretic exposure. Preserved urine output (>0.3 ml/kg/h) and a net negative fluid balance during CRRT were associated with achieving more RRT-free days and lower $MAKE_{30}$ (adjusted OR: 0.16; 95% CI: 0.09–0.29) in a retrospective cohort of 371 critically ill children.[1008] Children who did not successfully discontinue RRT had longer ICU stays and higher in-hospital mortality.[1008]

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CHAPTER 6. FOLLOW-UP CARE AFTER AKI OR AKD

Robust epidemiological data have revealed that people with CKD are at increased risk of AKI, and those who survive AKI and/or AKD face heightened long-term risks of CKD, cardiovascular events, recurrent AKI, and premature mortality, confirming a bidirectional relationship between AKI, AKD and CKD. Emerging evidence suggests that systematic approaches to post-AKI care, including nephrology follow-up, medication optimization, and structured surveillance protocols, may mitigate some of these adverse outcomes. This chapter synthesizes recent advances in management post-AKI/AKD and follow-up care to improve long-term outcomes.

6.1 Planning follow-up care with people after AKI and/or AKD

Recommendation 6.1.1: We recommend coordinated follow-up for children and adults after AKI and/or AKD, with personalized care according to individual clinical context and vulnerability risks (*1B*).

This recommendation places a high value on the potential benefits of individualized risk assessment to deliver personalized care for children and adults following an episode of illness affected by AKI and/or AKD. There is consistent evidence that AKD and all stages of AKI are associated with adverse long-term outcomes. The recommendation recognizes that people affected by AKI and/or AKD are heterogenous with varying needs and priorities. As a clinical syndrome, AKI offers an opportunity to improve systems of care and outcomes for people living with complex health needs. To achieve this, the recommendation encourages healthcare professionals, patients (and carers), researchers, and policy makers to consider implementing strategies that maximize the clinical utility of AKI as a marker of systemic vulnerability and adverse outcomes, while minimizing the potential for treatment and workload burden. There is insufficient evidence favoring one provider type or model of care over any other; consequently, individual patient, healthcare professional, and local system factors, including availability and expertise, are likely the best drivers of these decisions.

Key information

Balance of benefits and harms.

There is extensive evidence that AKI/AKD is associated with poor outcomes.[59, 61, 1017, 1146-1154] Relevant health outcomes for children and adults with AKI and/or AKD go beyond the initial episode of acute illness with a need to plan timely and tailored follow-up care to reduce the risks, in the short, medium, and long-term, of adverse kidney and non-kidney outcomes (Table 57). Reducing the risk of all-cause hospital readmission and mortality are immediate outcomes for consideration.[1155, 1156] Longer term adverse outcomes include *de novo* CKD, CKD progression, kidney failure, and further episodes of AKI,[1150, 1157] as well as development of hypertension and cardiovascular disease (CVD). Physical, psychological, and social support are also central to improving functional status and QoL.[1158-1161] In addition, a systematic review that compared the out-of-pocket payments for various conditions identified

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kidney disease, including AKI. as the leading cause of catastrophic health expenditure across lower-resource settings.[742]

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Table 57 | Monitoring for adverse outcomes after AKI and/or AKD requiring follow-up care

Domain	Outcome	Population	Rationale for follow-up
Within 3 months			
Kidney health	Proteinuria/albuminuria, kidney function	Children and adults	Proteinuria/albuminuria: Marker of sustained damage. Readily available, underutilized Kidney function: need early evaluation of kidney function, especially in cases of incomplete resolution of AKI where further diagnostic testing may be warranted, or where kidney function remains dynamic at time of discharge
Cardiovascular health	Hypertension, decompensated heart failure	Children and adults	Hypertension: Common post-AKI sequela, may be under-recognized without regular monitoring, especially in pediatrics. Decompensated heart failure: Common cause of readmission post-AKI
Physical function	Physical deconditioning, reduced mobility	Children and adults	ICU stay and AKI-associated immobility may impair functional recovery.
Psychosocial	PTSD, anxiety, family distress	Children and adults	AKI and ICU exposure are associated with increased mental health challenges and caregiver burden.
Healthcare utilization	Increased rehospitalizations, medication burden	Children and adults	AKI increases healthcare utilization, especially in medically complex pediatric cases.
Quality of life	Impact on quality of life, especially in case of progressive CKD and long-term dialysis dependence	Children and adults	Consequences of AKI can affect quality of life and well-being, including that of caregivers.
At 3 months or beyond			
Kidney health	Development and/or progression of CKD, proteinuria/albuminuria	Children and adults	AKI is a risk factor for CKD; risk stratification may differ by age. Proteinuria/albuminuria: predictor of progression of kidney disease. Readily available, underutilized
Cardiovascular	Hypertension, heart failure, cardiovascular events	Predominantly adults	AKI is an independent risk factor for CVD and hospital readmission, particularly readmissions with acute pulmonary edema.
Neurocognitive function	Neurodevelopmental delay, cognitive impairment, behavioral challenges	Predominantly children	AKI increases the risk of delirium in adults and may contribute to long-term brain health issues in pediatric survivors.
Growth and nutrition	Growth delay, malnutrition	Children	Undernutrition and fluid imbalance during AKI may impair linear growth.

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Socioeconomic	Loss of job security or gainful employment	Predominantly adults but also affects parents of children with AKI	AKI-related disability or chronic health issues may impair workforce return and contribute to financial insecurity. In countries where patients pay for medical treatment, AKI-related costs can lead to rapid impoverishment.

AKD, acute kidney disease; AKI, acute kidney injury; CKD, chronic kidney disease; CVD, cardiovascular disease; ICU, intensive care unit; PTSD, post-traumatic stress syndrome

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Acute management of AKI and/or AKD without coordinated planning of timely follow-up care has the potential to exacerbate patient harm. Risks in the short-term include the potential for unplanned hospital readmission due to inadequate early post-AKI clinical assessment (including BP and fluid status to ensure euvolemia) following suspension of diuretics and other cardiovascular medication during an episode of acute illness;[1162] failure to ensure ongoing monitoring and management for people without resolution of AKI/AKD; and inadequate follow-up to address underlying causes and vulnerabilities (e.g., frailty, social needs including limited access to housing, food, transportation, and financial stability).[1159, 1161] In the longer-term, potential harms might stem from inadequate evaluation for CKD and ongoing assessment to determine the risks and benefits of initiating or restarting drugs of cardiovascular prognostic benefit, particularly in adults.[1163-1166] Without a comprehensive approach that entails patient engagement, which places AKI in the context of supporting a person's physical and mental health to enable recovery in social functioning, there remains a risk that post-AKI care may result in unnecessary treatment burden and duplication of clinical workload.[1158, 1159, 1166-1170]

Potential psychosocial harms from clinical reassessment following AKI have been reported by patients and include the treatment burden of post-hospitalization care resulting from additional clinic visits, strain on patients and caregivers, and financial pressure because of medical expenses.[1169] Patients have described anxiety from competing health demands as challenges.[1168] Approaches that alleviate treatment burden while implementing a comprehensive model of care may be more acceptable.

The systematic review for this guideline identified that interventions to implement comprehensive post-AKI care were associated with reduced mortality (1 RCT and 3 observational studies; RR: 0.75; 95% CI: 0.70–0.81) and a reduced risk of CKD requiring maintenance dialysis (one observational study, HR: 0.58; 95% CI: 0.54–0.62), with uncertain effects on other outcomes (Supplementary Table S92).[1171-1174] In an RCT, 98 participants with AKI were randomized to comprehensive multidisciplinary nephrology care (5 visits) versus standard care for 12 months post-discharge.[1173] Nephrologists were the principal physicians providing coordination with other healthcare professionals to manage all transition care post-AKI. This trial reported better BP control and lower UACR in the nephrology care group, but there was no difference in mean eGFR or other kidney outcomes between the 2 groups at one year.

Several observational studies have highlighted gaps in follow-up care processes for children and adults affected by AKI/AKD, reflecting missed opportunities across healthcare systems.[1175, 1176] However, there remains limited trial-based evidence on models to enhance implementation of these recommended actions. Meta-analysis combining 5 observational studies and 1 RCT in adults found that nephrology follow-up was associated with a lower risk of death (RR: 0.84; 95% CI: 0.76–0.93) and possibly lower risk of recurrent AKI (RR: 0.57; 95% CI: 0.33–1.01; Supplementary Table S93).[1177-1179] In particular, one study reported that among adults who had received temporary dialysis during an admission with AKI, early nephrology follow-up was associated with lower mortality.[1180] However, the observational

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studies included in this review consistently found that adults who had nephrology follow-up were more likely to ultimately receive maintenance dialysis (CKD G5D); the reason for this is unclear, but may relate to unaccounted confounding with the likelihood that people with more advanced kidney disease post-AKI may be more likely to be followed by a nephrologist.[1180]

Children with a history of AKI are also at increased risk for long-term kidney sequelae, including recurrent AKI, proteinuria, hypertension, and progression to CKD, yet most do not receive structured nephrology follow-up.[1176] In a systematic review encompassing over 6700 children with cardiac disease undergoing cardiac surgery, subclinical injury markers, such as proteinuria and tubular damage biomarkers were common after AKI, even without overt CKD, but nephrology follow-up occurred in fewer than 5% of cases, underscoring the need for standardized surveillance protocols that incorporate risk stratification by AKI severity and cardiac complexity, with long-term monitoring that extends beyond SCr alone.[1153]

Certainty of evidence

There is moderate certainty of evidence that comprehensive care post-AKI in adults is associated with reduced risk of death and maintenance dialysis (with low certainty of evidence), with uncertain effects on other kidney-related outcomes.[1171-1174] The certainty of evidence was downgraded for methodological quality (including mostly nonrandomized trials) and for maintenance dialysis, sparseness of studies. The overall certainty of evidence was graded as moderate based primarily on certainty regarding mortality.

There is low certainty of evidence that follow-up by a nephrologist, specifically, in adults post-AKI is associated with lower risk of death and possibly recurrent AKI; although, with a higher incidence of maintenance dialysis reported among people seen by nephrologists.[1177-1179] The certainty of evidence was downgraded for methodological quality of mostly observational studies.

No eligible studies were conducted in children. However, the Work Group felt that the findings in the adult literature were applicable to pediatric populations and did not rate the findings any lower for indirectness when applied to the pediatric population.

Values and preferences.

A systematic review of patient experiences has highlighted major challenges for people following an episode of illness affected by AKI. Difficulties include navigating fragmented systems of care after hospital discharge; reduced well-being with limited ability to carry out daily activities; uncertainties surrounding resolution of AKI; dealing with competing health priorities; and unsustainable treatment burden associated with ongoing monitoring.[1181, 1182] People often lack awareness of their AKI diagnosis.[1169, 1183-1185] Supporting people during this period of vulnerability to gain confidence in self-management, with a focus on understanding and optimizing kidney health protection strategies in the

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context of addressing wider health and social needs, is a key element of follow-up care after AKI and/or AKD.[1169]

Resource use and costs.

The systematic follow-up of AKI survivors is associated with increased resource use entailing additional laboratory testing, a nephrology workforce as well as a range of multidisciplinary healthcare professionals. This may lead to increased rates of rehospitalization and referral through earlier detection of adverse events. These costs may be offset by better longer-term outcomes for AKI survivors, although this has not yet been proven in RCTs.

Considerations for implementation.

Barriers to follow-up care include under-recognition of AKI by healthcare professionals, lack of knowledge about the systemic and life-course impact of AKI by the healthcare team, insufficient patient and healthcare professional knowledge about AKI and its attendant risk, challenges integrating AKI and kidney health into the context of competing priorities of care for comorbidities, a lack of evidence for effective interventions to improve outcomes after AKI, and limited timely access to nephrology care. The role and resourcing of primary care as well as the use of virtual or point-of-care follow-up strategies focused on those at highest risk of short-term and long-term adverse outcomes may more effectively target AKI survivors who are most likely to benefit but requires further evaluation. Implementation should consider the use of approaches that alleviate treatment burden for patients while delivering comprehensive and integrated models of care that improve patient outcomes.

Rationale

AKI is a common, harmful and costly clinical syndrome. It is a marker of systemic vulnerability, with evidence of adverse kidney and non-kidney outcomes across all stages of AKI. Significant gaps have been identified in the post-discharge care of AKI survivors.[1181] Prior research has demonstrated that several domains of care could be improved for follow-up care of people with AKI/AKD.

CKD assessment and management following AKI often falls short of best practices, with many adults not receiving statins or RASi, despite evidence they can improve kidney and cardiovascular outcomes.[1165, 1186-1188] Recognition and follow-up of AKI after discharge is poor due to deficits in communication about AKI, lack of healthcare professional recognition of people at risk of adverse sequelae from AKI after hospital discharge, and an already high burden of care and complexity due to comorbidities. Adults describe prioritization of conditions other than AKI, variability in comprehension of the significance of AKI and kidney health, and anxiety from discharge planning and competing health demands, while healthcare professionals have identified care coordination and communication as key challenges to providing effective care.[1169, 1181]

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Appropriate clinical oversight is necessary to support the development and effective communication of a discharge plan that clarifies the purpose and timing of clinical follow-up including the implementation of kidney health protection strategies (e.g., monitoring of kidney health status and medicines optimization). Furthermore, people affected by AKI often feel vulnerable and in the context of reduced patient and system capacity may benefit from support coordinating timely multiprofessional follow-up.[1169] Organizing early clinical follow-up prior to discharge is necessary for those at high risk of hospital readmission. Clarity on the purpose of follow-up at 3 months after discharge needs to be clearly communicated with people affected by AKI/AKD and care professionals including those in primary care.

Based upon best available evidence, consensus guidance highlights key actions required to improve AKI and/or AKD aftercare in both high- and low-resource settings. To maximize clinical utility and minimize treatment burden, AKI and/or AKD need to be placed in clinical and social context with coordinated follow-up care needing to take into account: patient-specific risk factors; characteristics of the AKI episode; and the degree of resolution of AKI/AKD. A holistic approach considers the interaction between emotional, cognitive, and social vulnerabilities with the severity of the illness event and underlying comorbidities (Figure 20).[1159]

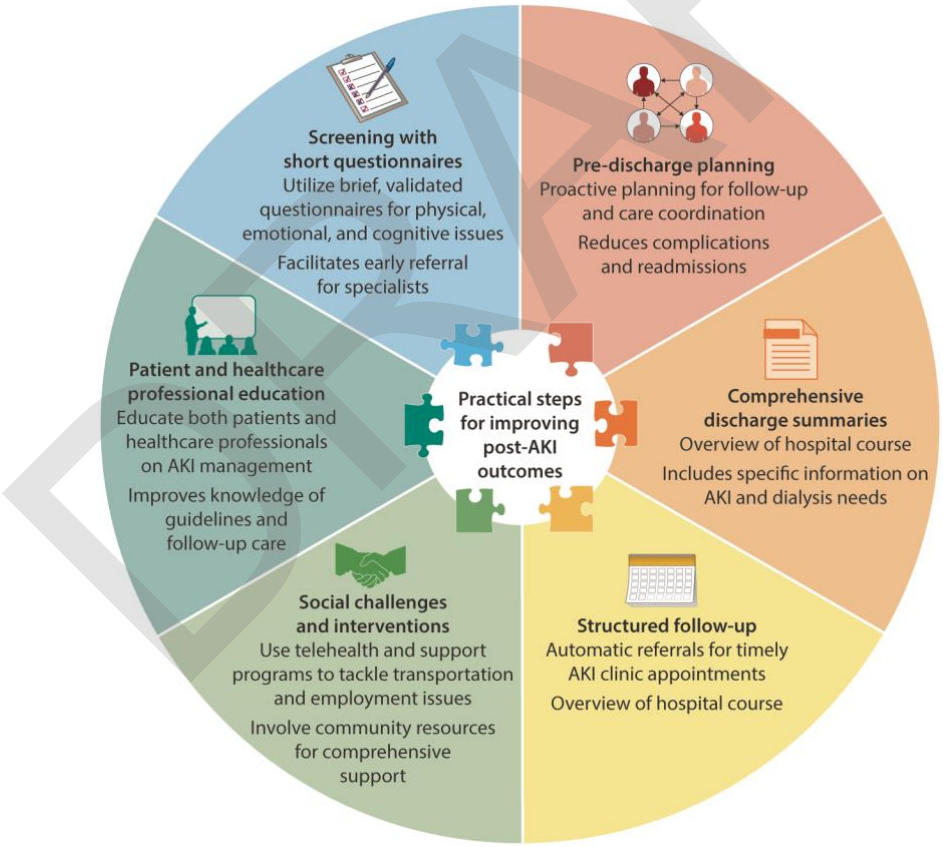
Screening with short questionnaires
Utilize brief, validated questionnaires for physical, emotional, and cognitive issues
Facilitates early referral for specialists
Pre-discharge planning
Proactive planning for follow-up and care coordination
Reduces complications and readmissions
Patient and healthcare professional education
Educate both patients and healthcare professionals on AKI management
Improves knowledge of guidelines and follow-up care
Practical steps for improving post-AKI outcomes
Comprehensive discharge summaries
Overview of hospital course
Includes specific information on AKI and dialysis needs
Social challenges and interventions
Use telehealth and support programs to tackle transportation and employment issues
Involve community resources for comprehensive support
Structured follow-up
Automatic referrals for timely AKI clinic appointments
Overview of hospital course

Figure 20 | Strategies to deliver holistic follow-up care with children and adults after AKI/AKD.[1159] AKD, acute kidney disease; AKI, acute kidney injury

AKD affects a substantial proportion of children following AKI, with reported incidence ranging from 17% to >50%, and consistently predicts adverse outcomes, including CKD. Risk factors for AKD and its progression include higher AKI severity and duration,

persistent oliguria, anemia, glomerulonephritis, tubulointerstitial nephritis, and the need for RRT. Critically ill children have a particularly high burden of AKI and AKD. Importantly, AKD is predictive of MAKE and reduced eGFR at both 90 days and longer-term follow-up, even among children without prior AKI.[62, 1189-1193] This suggests that AKD is a clinically relevant, high-risk condition that warrants structured post-discharge monitoring to mitigate progression to CKD in children.

Special considerations

Adults with heart failure. Recognizing that a high proportion of readmissions relate to people with pulmonary edema, post-AKI care needs to be aligned with and build on evidence underpinning heart failure management.[1155, 1156, 1194, 1195] In people with heart failure, caution is necessary when interpreting kidney function tests (including changes in eGFR) as rises in SCr are common and may reflect changes in hemodynamics (for instance, after initiation of RASi or SGLT2i) rather than be due to intrinsic kidney injury.[1196-1198] As such, placing kidney function tests in clinical context is essential, with decongestion and assessment of volume status to achieve "clinical euvolemia" being key elements of post-AKI care to improve outcomes.[1196]

Practice Point 6.1.1: Transition of care from hospital to home requires clear communication between inpatient and outpatient care teams, an identified healthcare professional for AKI follow-up, and resources for patient engagement and education about their kidney health and kidney health protection.

Incorporating specific kidney health protection plans into follow-up care pathways requires communication between inpatient and outpatient healthcare professionals and coordinated planning with integration between healthcare professionals and clinical services. This may involve several healthcare professionals and other clinical services, such as postoperative care teams, comprehensive geriatric assessments for frail individuals, oncology, or heart failure services, in addition to primary care.

The timing of follow-up should be individualized based on patient-specific risk factors, comorbidities, the characteristics of the AKI episode (e.g., severity and duration), and the extent of AKI/AKD resolution. Guidance for CKD evaluation at 3 months post-AKI (Section 6.4) should be communicated and coordinated with the appropriate healthcare professional prior to hospital discharge. Early, coordinated follow-up is particularly important for people who: have a high risk of hospital readmission due to comorbid conditions (e.g., heart failure, frailty) or a significant acute illness (e.g., episode of temporary RRT, ICU admission); require early clinical review to assess BP, volume status, or to safely reintroduce or dose adjust medications withheld during hospitalization or introduce new kidney-protective medications; need early evaluation of kidney function, especially in cases of incomplete resolution of AKI where further diagnostic testing may be warranted, or where kidney function remains dynamic at time of discharge; and/or for people experiencing social vulnerability, which may impact their ability to access or adhere to follow-up care.

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Early follow-up appointments are ideally scheduled prior to hospital discharge to ensure timely post-acute care. Care coordinators and/or nurse navigators can play a key role in supporting care transitions by promoting continuity, delivering kidney health education, and minimizing treatment burden from multiple healthcare professionals, while ensuring that follow-up care remains aligned with the person' goals, values, and preferences.[1199] This includes facilitating coordinated follow-up for patients discharged to other institutions, rehabilitation, or convalescent facilities.

There is also growing literature and expert consensus supporting the involvement of pharmacists, both in the inpatient and outpatient setting and in collaboration with primary care teams, to enhance medication management and optimize follow-up care after AKI/AKD.[1200]

Practice Point 6.1.2: Provide discharge summaries for children and adults with AKI that include details of the AKI episode, status of the resolution of AKI, medication management, and follow-up plans with recommendations.

AKI is frequently under-recognized and poorly documented at discharge, especially in children.[1201, 1202] Studies have also shown that AKI is often not identified in primary care records, leading to loss of the diagnosis during care transitions and limiting ongoing management, including during future episodes of acute illness.[1176, 1190, 1203] Most adults affected by AKI are unclear on the diagnosis and its relevance. Caregivers for children may also be unaware their child experienced AKI and targeted education is often lacking. In a recent cross-sectional study, 75% of caregivers were unaware their child had experienced AKI, and fewer than 40% recalled any discussion of kidney injury during the hospitalization. Nephrology consultation improved recognition, but substantial knowledge gaps persisted across services.[1204] For both children and adults, standardized discharge summaries should include details of the AKI episode, status of the resolution of AKI, medication management including reasons for medication changes and guidance regarding if, when, and how to initiate or restart drugs, with a follow-up plan outlining ongoing monitoring of kidney health status.

Given the high frequency of comorbid conditions and multidisciplinary outpatient care, effective information-sharing is essential, not only with general practitioners and pediatricians providing primary care, but also with relevant subspecialists such as cardiology, transplant, or oncology, including specialist nurses. Embedding kidney health monitoring into these care pathways, along with clear guidance on when to refer back to nephrology, is expected to enhance patient experience and continuity of care.[1176]

To address these major gaps in follow-up care, multiprofessional models that entail early and ongoing patient education, beginning during admission and reinforced at follow-up visits in primary care have been developed, with findings to date demonstrating improvements in care processes and patients' knowledge of kidney health.[1205-1207] Furthermore, audit and feedback interventions in conjunction with multiprofessional

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education, leading to the development of systems-level improvement plans show promise and warrant further evaluation.[1202, 1206, 1208, 1209]

Practice Point 6.1.3: A comprehensive clinical assessment of children and adults following an episode of illness affected by AKI/AKD includes assessment of blood pressure (BP) and volume status, medication reconciliation/review, and kidney function and albuminuria after hospital discharge.

AKI survivors have a high rate of rehospitalization and significantly elevated risks of major adverse cardiovascular and kidney events.[207, 1146, 1160] Although interventional evidence is currently low, a standardized approach to assessment may address observed care gaps in AKI survivors. Informed by best available evidence, consensus work has provided guidance regarding the timeliness and intensity of follow-up as well as "what" follow-up care after AKI/AKD should entail. The Kidney function check, Advocacy, Medications, Pressure, Sick day protocols (KAMPS) framework (Table 58) identifies key actions that support the health and wellbeing of people who have had an AKI/AKD event.

Table 58 |.Post-AKI/AKD kidney health care framework[1210]

KAMPS Framework	Components
Kidney function check	Measure kidney function (e.g., serum creatinine or cystatin C), urinalysis, assessment of albuminuria
Advocacy	Patient education about kidney function and AKI, what to expect in resolution of AKI, and self-care strategies
Medications	Medication review and reconciliation
Pressure	Blood pressure evaluation and adherence to guideline-recommended targets
Sick day protocols	Patient information about how to self-manage medications in the event of dehydration or acute illness

AKD, acute kidney disease; AKI, acute kidney injury

Comprehensive assessment of kidney function includes evaluation of eGFR (e.g., SCr, cystatin C) as well as albuminuria. BP control and volume assessment are particularly important in the post-AKI period as antihypertensive medications and diuretics are frequently stopped or modified during an AKI event.[1211, 1212] A Canadian cohort study showed that heart failure accounted for 13% of the primary hospital readmission diagnoses.[1156, 1162, 1213, 1214] A cohort study in Scotland found that 26.6% of rehospitalizations at 90-days related to acute pulmonary edema.[1155]

Medication review, reconciliation, and adjustment, if necessary, can be provided by many healthcare professionals, including pharmacists, and primary care physicians. The original clinical indication for a drug should be reviewed. If a specific contraindication for a drug has been identified, this should be documented and an alternative medication should be considered.

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Practice Point 6.1.4: Provide children and adults (and their caregivers) with a history of AKI and/or AKD access to education about kidney health, sick day guidance and kidney care, and psychosocial support to enhance functional status and quality of life.

Patients and caregivers often lack awareness of the long-term consequences of AKI/AKD and may not recognize the importance of ongoing monitoring or early intervention during intercurrent illness.[1181] Children and adults who have sustained AKI and/or AKD are at risk of recurrence. Educational efforts should include recognition of early warning signs, appropriate fluid and medication management during illness, and guidance on when to seek medical attention. Structured education addressing kidney health can empower patients and families to actively participate in resolution of AKI and long-term self-care. Tailoring this educational content to developmental stage, health literacy, and local context enhances engagement and may reduce disparities in outcomes following AKI.

People require ongoing education about their kidney health including the rationale for eGFR and UACR monitoring as well as best practices for kidney care including diet and lifestyle recommendations.[1207] Different online resources exist but it is important to tailor them to the patient population and healthcare setting. An example is https://www.thinkkidneys.nhs.uk/aki/wp-content/uploads/sites/2/2016/07/Infographic-poster-March-2017.pdf

Support to optimize medication management (Section 7.3) includes avoidance of NSAIDs and minimization of other nephrotoxic drugs, unless the benefits outweigh risks and there is no alternative. Recognizing the association between AKI and frailty, interventions to improve muscle mass/strength may be beneficial to enhance functional outcomes and warrant further evaluation.[1215-1218]

Kidney health protection strategies should include communication about possible causes of AKI, how to maintain fluid balance during an acute illness, and when to seek medical attention. Guidance on supporting medication management for adults during an episode of acute illness requires an individualized risk assessment, considering a person's capacity to self-manage.[1219-1221] Recommendations and practice points related to temporarily withholding specific classes of drugs in the setting of acute illnesses that predispose to hypovolemia or hypotension (SDMG) are provided in Chapter 4 (Section 4.11) and also apply in the period following an episode of AKI or AKI. Patient self-management strategies for SDMG should be provided in conjunction with support from healthcare professionals[684, 1219] and reinforced during hospital discharge, follow-up visits, and transitions in care.

Given the association between AKI and long-term physical and cognitive impairment, educational interventions should also address rehabilitation strategies, including promotion of physical activity and nutritional support to preserve muscle mass and support neurodevelopmental recovery. Pediatric AKI education programs should center the child and family, with kidney health advocacy integrated into broader child health and non-communicable disease initiatives.[1222]

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Recommendation 6.1.2: We suggest risk stratification of AKI survivors at hospital discharge using a validated tool to identify children and adults at high risk of CKD who may benefit from nephrology care after AKI *(2D)*.

This recommendation and related practice point place a high value on assessing a person's risk of severe CKD to determine the most appropriate form of follow-up care following AKI/AKD, recognizing a need to ensure children and adults are seen by the appropriate clinical professionals, in the right setting and at the right time according to their physical, psychological, and social needs and preferences. The recommendation aims to optimize resource allocation and minimize treatment burden, particularly in terms of who is likely to benefit most from nephrology care following hospital discharge after AKI/AKD.

Key information

Balance of benefits and harms

A Canadian trial randomized adults with a history of Stage 2–3 AKI to receive a risk-stratified intervention guided by a validated risk index to predict risk of severe CKD versus usual post-discharge care (Supplementary Table S94).[1223] In the risk stratified group, high-risk participants received follow-up with a nephrologist and low-risk participants were followed up by primary care physicians with recommendations provided. The trial found that this strategy increased nephrology follow-up for those participants with sustained eGFR<30 ml/min per 1.73 m^2 (RR: 3.17; 95% CI: 1.45–6.95).[1223] There was also greater use of RASi and statins when clinically indicated in the group at high risk of severe CKD among those who received the risk-stratified follow-up intervention, but without evidence of differences in development of CKD G5, need for long-term dialysis, or mortality (Supplementary Table S92).[1224] When using a composite processes of care outcome consisting of nephrology follow-up among people with CKD at 90 days post hospital discharge and adherence to the management recommendations for ACEi/ARBs and statins, risk-based follow-up was associated with significantly better care delivery (RR: 9.34; 95% CI: 2.58–43.62).[1223]

There are a number of ongoing RCTs in progress in North America evaluating the clinical effectiveness of interventions to improve follow-up care after AKI.[1123, 1205, 1225]

Certainty of evidence

There is very low certainty of evidence, based on a single small study, that use of risk-stratification to guide care improves some measures of quality of care (i.e., RASi and statin use, nephrology follow-up) among adult survivors of AKI at high risk of severe CKD, but no effect has been demonstrated on individual prioritized kidney-related clinical outcomes in adults.[1223] The certainty of evidence was downgraded for sparseness, imprecision, and methodological limitations (lack of blinding).

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Values and preferences

There is broad agreement that follow-up care after AKI/AKD should be multiprofessional, with kidney health protection plans developed prior to hospital discharge and tailored to people's overall care needs. This recommendation places a high value on optimizing care for AKI survivors with or at risk of CKD. Targeted follow-up for people at higher risk of CKD following AKI makes efficient use of both nephrologist and primary care, providing evidence-based therapies aimed at reducing kidney disease progression and cardiovascular consequences, such as use of RASi, statins, and SGLT2i.[1165, 1226] This approach also aims to minimize the burden of follow-up (i.e., anxiety, financial, employment, time) for low-risk patients and their caregivers.

Resource use and costs

There is insufficient capacity within the global nephrology workforces to see all AKI survivors, with a need to largely place AKI in the context of enhancing comprehensive, person-centered generalist care. A risk-stratified approach to follow-up, intensifying resource use for those at highest risk of CKD, can optimize nephrology resource allocation and help ensure people receive care from the appropriate team, in the right setting, and at the right time without overburdening low-risk patients.

Considerations for implementation

Identification of people with AKI/AKD who benefit most from follow-up care after hospital discharge remains challenging in clinical practice. A validation study of risk models demonstrated that greater net benefit was achieved when follow-up decisions were based on a risk prediction model for severe CKD after AKI rather than strategies based only on AKI severity or kidney function at discharge.[1227] In future, integration of risk calculation tools into routine hospital workflows may facilitate uptake but needs to be linked with proper training and support for healthcare professionals to interpret risk scores and determine appropriate follow-up care pathways. Resource allocation, such as ensuring timely access to nephrology services for high-risk people, is also needed to facilitate timely care.

Risk models that accurately estimate the probability of severe CKD following AKI are available to identify survivors of AKI who may benefit from nephrology care. James *et al.* derived and externally validated a predictive model for advanced CKD (G4 or G5) after an episode of AKI.[1228] (Figure 21) The 6-variable model (including age, gender, baseline SCr, albuminuria, AKI severity, and SCr at hospital discharge as predictors) was well calibrated and achieved a C-statistic of 0.81 (95% CI: 0.75–0.86) in the validation cohort. [1228]

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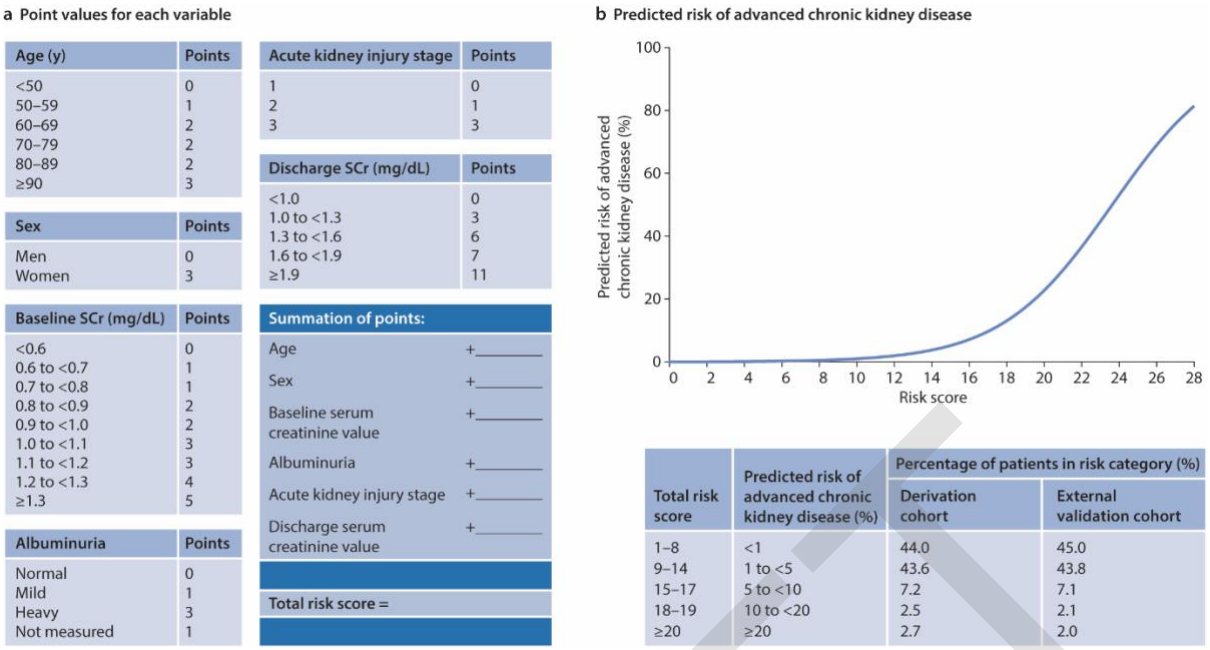
a Point values for each variable
Age (y) | Points
<50 | 0
50–59 | 1
60–69 | 2
70–79 | 2
80–89 | 2
≥90 | 3
Sex | Points
Men | 0
Women | 3
Baseline SCr (mg/dL) | Points
<0.6 | 0
0.6 to <0.7 | 1
0.7 to <0.8 | 1
0.8 to <0.9 | 2
0.9 to <1.0 | 2
1.0 to <1.1 | 3
1.1 to <1.2 | 3
1.2 to <1.3 | 4
≥1.3 | 5
Albuminuria | Points
Normal | 0
Mild | 1
Heavy | 3
Not measured | 1
Acute kidney injury stage | Points
1 | 0
2 | 1
3 | 3
Discharge SCr (mg/dL) | Points
<1.0 | 0
1.0 to <1.3 | 3
1.3 to <1.6 | 6
1.6 to <1.9 | 7
≥1.9 | 11
Summation of points:
Age +_____
Sex +_____
Baseline serum creatinine value +_____
Albuminuria +_____
Acute kidney injury stage +_____
Discharge serum creatinine value +_____
Total risk score =
b Predicted risk of advanced chronic kidney disease
Predicted risk of advanced chronic kidney disease (%)
100
80
60
40
20
0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28
Risk score
Total risk score | Predicted risk of advanced chronic kidney disease (%) | Percentage of patients in risk category (%) | |
| | Derivation cohort | External validation cohort
1–8 | <1 | 44.0 | 45.0
9–14 | 1 to <5 | 43.6 | 43.8
15–17 | 5 to <10 | 7.2 | 7.1
18–19 | 10 to <20 | 2.5 | 2.1
≥20 | ≥20 | 2.7 | 2.0

Figure 21 | 6-variable risk score to predict transition to severe CKD (G4 or G5) for adults after hospitalization with AKI.[1228] AKI, acute kidney injury; CKD, chronic kidney disease

Clear communication strategies with patients about their risk status and the importance of follow-up care are important. Ongoing monitoring of a risk model's performance and adherence to follow-up protocols can help refine processes, ensuring that people most likely to benefit from nephrology care receive appropriate support.

Rationale

There is a significant gap between the need for nephrology care and the available global nephrology workforce.[1229] Given the high global incidence of AKI, it is not feasible for every AKI survivor to receive AKI care from a nephrologist, therefore identification of people most likely to benefit from nephrology care optimizes the use of these limited resources. Fewer than 5% of adults with AKI see a nephrologist after hospital discharge, including <30% of those who subsequently develop CKD within a year after hospitalization.[1230] Nephrology follow-up after pediatric AKI is also infrequent, even among those with severe AKI, despite known risks for CKD and hypertension.[1176, 1231]

Many of the recommendations for follow-up of AKI survivors can be effectively provided by non-nephrology healthcare teams, including primary care in collaboration with allied healthcare professionals (pharmacists, nurses, dieticians, social workers, social-prescribing teams, community health workers). However, it is likely that some people may specifically benefit from nephrology care, particularly those at high risk for major adverse kidney outcomes (e.g., *de novo* CKD or CKD progression). Aligning use of nephrology services to a person's risk of developing severe CKD has the potential to reduce treatment burden for low-risk patients and better optimize nephrology follow-up care for those with greatest need. Reducing the intensity of follow-up for low-risk patients acknowledges that not

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all people develop CKD and that adults may encounter barriers to follow-up care, including hospitalization related-fatigue, a reluctance to see more doctors, and long travel times.[1167, 1169]

Most patients receive follow-up with other physicians, indicating opportunities for knowledge translation and surveillance to be integrated into subspecialty care or general medical clinics for people at low risk of severe CKD. Given that nearly all AKI survivors engage with the healthcare system post discharge, targeted knowledge translation and implementation of pragmatic follow-up strategies, especially for non-nephrologists, are essential to ensure appropriate long-term kidney monitoring and intervention.

6.2. Medication management following AKI and/or AKD

Recommendation 6.2.1: We recommend starting or resuming RASi in adults, unless there is a contraindication, in accordance with evidence-based guideline indications *(adults: 1B; children: 1D)*.

This recommendation places a high value on the benefits of evidence-based therapies to treat diabetes, cardiovascular disease (including heart failure), and CKD; all of which are common comorbidities in children and adults with AKI and may also contribute to the development of AKI. Observational studies report better survival among adults resuming or starting these medications after an episode of AKI and/or AKD. This recommendation aligns with the KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of CKD (Sections 3.6) for specific recommendations and practice points in relation to RASi.[1164] Although there is very little evidence in children, the Work Group felt this recommendation would also apply to children.

Key information

Balance of benefits and harms

The effectiveness of RASi treatment as a strategy to prevent adverse outcomes after AKI/AKD has not been evaluated in randomized trials; however observational studies have reported lower mortality among people who resumed these medications than those who did not following a hospitalization with AKI. Some observational studies have shown that treatment with RASi may increase the risk of hyperkalemia and readmission for AKI. In a randomized trial from Canada where more patients in the intervention arm received RASi after a hospitalization with AKI, there was a higher rate of hyperkalemia in the intervention arm, suggesting that close laboratory monitoring is required for safety.

An evidence review of 8 studies including 81,869 adults demonstrated that reinitiation of ACEi or ARBs after AKI was associated with a significantly lower mortality (HR: 0.83; 95% CI:0.75–0.91) and MACE (HR: 0.88; 95% CI: 0.85–0.92) without increasing the risk of recurrent AKI or MAKE (Supplementary Table S95).[1187, 1188, 1232-1237] Across 5 studies including 31,970 adults, newly starting ACEi or ARBs after AKI was also associated with significantly lower mortality (HR: 0.87; 95% CI: 0.81–0.95; Supplementary Table S96).[1165, 1233, 1235-1237]

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A multicenter retrospective cohort analysis from Taiwan evaluated the timing of RASi reinitiation after an AKI episode and observed that earlier reinitiation of these medications in adults within 3 months of discharge was associated with a lower hazard for mortality, cardiovascular events, and kidney failure, without an increased risk of severe hyperkalemia.[1238] The benefit of resuming these therapies was also seen among adult participants with an eGFR <30 ml/min per 1.73 m^2 where earlier initiation was associated with a lower risk of dialysis or kidney failure. Other observational studies have reported lowest mortality when RASi was started in the initial month after AKI among adults with diabetes and proteinuria, regardless of whether the medication was started before or after resolution of AKI.[1014]

Certainty of evidence

There is moderate certainty of evidence that reinitiation of ACEi or ARBs after an episode of AKI reduces the likelihood of death and MACE, with no evidence of effects on likelihood of recurrent AKI, other AKI-related conditions, or poor control of underlying conditions other than MACE in adults. The certainty of evidence was downgraded for methodological quality of nonrandomized studies.[1187, 1188, 1232-1237]

There is moderate certainty of evidence that newly starting ACEi or ARBs after an episode of AKI reduces the likelihood of death, with low to moderate certainty of evidence of no evidence of effects on likelihood of AKI-related conditions in adults. Studies did not report on outcomes related to poor control of underlying conditions. The certainty of evidence was downgraded for methodological quality of nonrandomized studies and imprecisions of some AKI-related outcomes.[1165, 1233, 1235-1237]

Values and preferences

This recommendation places a high value on preventing future adverse health outcomes in AKI/AKD survivors. Diabetes, cardiovascular disease, heart failure, and CKD are common comorbidities in people who experience AKI and may contribute to recurrent AKI; ensuring that these conditions are effectively managed after an AKI episode is a key priority and is associated with better health outcomes.

Resource use and costs

Starting or restarting these therapies may involve short-term costs for people with respect to medication prescription and monitoring. However, this must be measured against long-term costs to patients and healthcare systems related to rehospitalization, cardiovascular morbidity and kidney events that may be potentially avoided.

Considerations for implementation

We recognize that care gaps exist in the treatment of chronic health conditions associated with AKI in adults and in particular in children. Further, the availability of healthcare professionals to recognize care gaps and address them is challenging in many parts of the world. Where possible, medication review and reconciliation should be integrated into routine follow-up care for people with AKI/AKD. Healthcare professional education is

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required to inform medication prescribers of the risks and benefits of starting or restarting RASi, and how to use them safely.

Rationale

Conditions benefiting from the use of RASi are prevalent in children and adults with a history of AKI/AKD. RASi are frequently stopped during an AKI event because of their effects on kidney hemodynamics and GFR, their association with hypotension, and the risk of hyperkalemia. In many patients, these drugs are not restarted after hospital discharge, despite clinal indications to do so, which is a potential gap in care.[1162, 1213]

Numerous retrospective cohort studies have evaluated the associations between ACEi or ARBs and clinical outcomes of people with AKI/AKD.[1239] A systematic review and meta-analysis of 7 retrospective cohort studies in adults reported lower all-cause mortality among ACEi or ARB users, including those who newly started or continued use after an AKI episode (OR: 0.37; 95% CI: 0.42 to 0.32) as well as an increased risk of hyperkalemia, however, there is an absence of evidence from RCTs on the effect of RASi initiation or reinitiation on other important clinical outcomes after an episode of AKI. Further, there is an absence of RCTs in children.

Practice Point 6.2.1: Evaluate the clinical indication for starting or resuming sodium-glucose cotransporter-2 inhibitors (SGLT2i), glucagon-like peptide-1 receptor agonists (GLP-1 RA) and mineralocorticoid receptor antagonists (MRA) in children and adults.

SGLT2i are indicated for use in children and adults with type 2 diabetes (T2D), CKD, and heart failure; all are common conditions among people who experience AKI. GLP-1 RAs also have been shown to have important effects on clinical outcomes in adults with T2D and CKD. These medications are frequently stopped during an episode of AKI due to a concern that they may exacerbate AKI due to their diuretic effects (SGLT2i) or gastrointestinal effects on oral intake (GLP-1 RA). Large retrospective cohort studies from Taiwan reported better outcomes with the use of SGLT2i and GLP-1 RA in people with diabetes and AKD.[1240 1241] These studies report a lower risk of all-cause mortality, major adverse kidney outcomes, and major adverse cardiac outcomes among people with clinical indications for restarting treatment.

MRAs are also commonly prescribed in populations at risk for AKI and are frequently stopped due to their association with hyperkalemia. Less is known about restarting MRA after an AKI event; however, given the range of demonstrated benefits over these disease states, cautious reinitiation of these medications after AKI in those with a clinical indication for treatment, no contraindications, stable kidney function, and an eGFR >25 ml/min per 1.73 m^2 should be considered.

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Practice Point 6.2.2: Assess the appropriateness of starting or resuming guideline-indicated medications at hospital discharge and by 3 months after AKI/AKD.

The optimal timing to restart medications after AKI/AKD is unknown. Reinitiation of medications should be considered in the overall context of the person and individualized based on comorbidities, resolution of acute illness, clinical assessment, and kidney function.[574] Diuretics and antihypertensive medications should be restarted when clinically indicated. Persistent electrolyte abnormalities or non-recovery of kidney function may preclude starting or restarting medications known to affect electrolyte balance, particularly those that affect serum potassium levels (i.e., MRA, RASi). If indicated, these medications should be restarted when kidney function and electrolyte balance stabilize, with a plan for frequent monitoring.

Practice Point 6.2.3: Monitor RASi, MRA, or diuretic prescription and management following AKI/AKD in accordance with the KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease.

The Work Group agrees with recommendations and selected practice points from the KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of CKD for the treatment of CKD with RASi, SGLT2i, GLP-1 RA, and MRA.[1164] This guideline provides specific information about drug dosing and monitoring of potassium and kidney function, after treatment initiation that apply to resumption following an episode of AKI/AKD.

6.3 Evaluation for CKD

Practice Point 6.3.1: Assess kidney function and markers of kidney damage 3 months after AKI or AKD to evaluate for resolution, and new onset or worsening of preexisting CKD.

Episodes of AKI and/or AKD are predictors for new or progressive CKD and kidney failure in children and adults, therefore assessments of both kidney function (SCr or cystatin C, eGFR, electrolytes) and kidney damage **(**UACR or urinary protein-to-creatinine ratio [UPCR]) 3 months after an AKI/AKD episode are important.[54, 57, 192] Furthermore, both reduced eGFR and albuminuria at 3 months are associated with subsequent progression of kidney disease.[57, 207, 528, 1150, 1242]

Recognizing that AKI, AKD, and CKD are related entities, monitoring for the development and progression of CKD is essential to improve kidney care and outcomes across this continuum of health states (Figure 22).[59, 528] Children and adults identified with CKD following AKI or AKD should be managed as detailed in the KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of CKD.[1164] Children and adults without CKD at 3 months remain at increased risk for new onset CKD and should also be managed according to the KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of CKD (Practice Point 1.1.1.1). Determining if, when, and how to initiate; restart; and uptitrate medication of clinical prognostic benefit for people with or at risk of

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CKD after an episode of AKI and/or AKD requires careful consideration, with assessment of eGFR, UACR, and electrolytes.

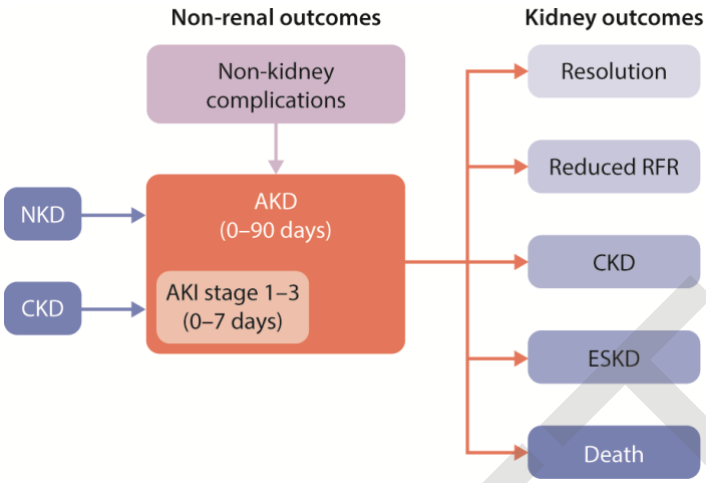

Figure 22 | Proposed conceptual model for the continuum of AKD, CKD, and AKI.[59]
AKD, acute kidney disease; AKI, acute kidney injury; CKD, chronic kidney disease

Practice Point 6.3.2: Serum cystatin C-based GFR estimation can be used to assess for CKD in children and adults after AKI in clinical situations where SCr is less accurate.

Muscle wasting is a common complication of prolonged hospitalization and is particularly prevalent in critical illness as well as other conditions commonly seen in people with AKI including cancer, malnutrition, heart failure, and cirrhosis.[1243] Cystatin C may be more accurate for estimating GFR than SCr among people who have had prolonged or critical illness and/or experienced significant weight loss or sarcopenia. The Work Group also refers to recommendations and selected practice points from the KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of CKD for the use of eGFRcr-cys.[1164]

In the context of hospitalized AKI, the use of SCr as a measure of kidney function and resolution of AKI may be confounded by reduction in muscle mass and changes in creatinine generation. This may result in an overestimation of kidney recovery in people with AKI/AKD.[20, 1017, 1243-1248] Cystatin C is independent of muscle mass and may be a better marker of kidney function in these people.

A prospective single center study of critically ill patients in the UK sequentially assessed kidney function using cystatin C, SCr, and measured GFR using iohexol, and found that eGFR by SCr systematically overestimated kidney function.[13] The AKI Risk in Derby (ARID) cohort study in the UK also demonstrated large discrepancies between eGFR based on cystatin C and eGFR based on SCr in a general hospitalized population at 3 months following discharge, with the magnitude in difference being more prominent in people affected by AKI.[1249]

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6.4 Post-discharge care for children and adults receiving RRT following AKI in the outpatient setting

Practice Point 6.4.1: RRT programs should incorporate comprehensive dialysis care and communication plans for children and adults receiving RRT following AKI tailored to their likelihood of dialysis liberation.

Up to 30% of adults who receive RRT for AKI and survive to hospital discharge will remain dialysis dependent at discharge, and of these, approximately half will be able to discontinue dialysis within 90 days.[1250] People who need ongoing RRT after hospitalization with AKI/AKD report inconsistent care in outpatient dialysis facilities where their care is frequently not distinguished from those receiving long-term dialysis for kidney failure. However, care goals for people receiving RRT after AKI often differ significantly from those receiving maintenance dialysis for chronic kidney failure, as recovery of kidney function is a desired outcome.

A specialized approach to care for people receiving short-term RRT in the outpatient setting may benefit patients, healthcare professionals, and healthcare systems. Patients may benefit from avoiding unnecessary harm of prolonged, unnecessary RRT if recovery of kidney function is identified. Those with a greater probability of resolution may benefit from additional monitoring procedures to identify recovery of kidney function and avoid prolonged, unnecessary RRT. Identification of people with a low likelihood of resolution may assist them, their caregivers, healthcare professionals, and healthcare systems in care planning discussions for long-term RRT and aid planning and resource allocation within dialysis units.

Prehospitalization kidney function is a strong predictor of dialysis independence; however, up to 30% of patients with baseline CKD G4 may also achieve dialysis independence post discharge.[812, 1251] Some predictive models have been published to better stratify the likelihood of discontinuing dialysis in adults following AKI.[1252]

Lee *et al*. developed and validated a prediction model for kidney recovery after AKI in a cohort of 2214 adults who started dialysis in hospital.[1252] Four factors were identified through stepwise regression as independent predictors of dialysis liberation: preadmission eGFR, preadmission hemoglobin, history of chronic liver disease, and age. This model excluded people with a >20% risk of inpatient mortality, only included preadmission and intra-admission variables, and did not account for the competing risk of death. It was also not externally validated and had relatively modest discrimination (C-index: 0.64).

Clark *et al*. developed and externally validated a predictive score for kidney recovery and death in patients continuing dialysis as outpatients after starting in hospital using a population based cohort of 7657 patient in Ontario Canada.[1253] Predictive variables identified in this analysis included comorbidities, days from admission to dialysis, days from first dialysis to discharge, ICU status, prehospital admission eGFR, and random UACR. While the ability of this tool to discriminate was modest (C-statistic: 0.7; 95% CI: 0.67–0.73 and 0.66;

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95% CI: 0.62–0.69 for the outcomes of recovery and death, respectively), the risk groups identified in the study did allow a degree of prognostic separation that may be clinically useful.

Practice Point 6.4.2: Engage patients, caregivers, and outpatient dialysis care teams in the development of a post-discharge care plan prior to transition from the hospital to community settings.

Practice Point 6.4.3: Dialysis care for children and adults receiving RRT following AKI requires clinical assessment of volume status, laboratory evaluation for evidence of kidney recovery, medication review and reconciliation, and patient education about identification of return of kidney function and minimizing kidney injury during the resolution phase.

Practice Point 6.4.4: Provide education and engage adults, children, and caregivers in shared decision-making focused around self-care, short- and long-term risks of permanent RRT and mortality, quality of life, and goals of care to inform decisions around dialysis care.

Transition to outpatient RRT requires timely transmission of discharge summaries, medication review and reconciliation, and recognition of potential for kidney function recovery to inform an appropriate monitoring plans. A post-discharge plan should engage patients, caregivers, and dialysis care professionals with clear roles and responsibilities (Table 59). Patient and caregiver education should be developmentally appropriate, culturally sensitive, and include individualized discussions on expectations for resolution, long-term risks, and care preferences.

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Table 59 | AKI receiving RRT follow-up multidisciplinary monitoring tasks

Assessment parameter	Patient/family task	Nurse	Nephrologist	PCP	Other team members
Serum creatinine (SCr)	Understand importance of lab trends; ask about recovery signs	Draw labs predialysis, monitor trends	Interpret SCr trends; determine recovery or weaning potential	Review labs if shared; monitor recovery during transitions	—
Blood urea nitrogen (BUN)	Understand BUN as a marker of nitrogenous waste levels; ask if safe to try off dialysis	Ensure predialysis BUN drawn and reported	Use BUN alongside clinical context to guide decisions	Track recovery trajectory and symptom changes	—
Electrolytes (K^+, HCO_3^-)	Adhere to potassium/bicarbonate-related diet and meds	Triage abnormal electrolyte results; reinforce dietary adherence	Adjust medications and dialysis based on electrolyte trends	Support medication adjustments during transitions	Pharmacist: adjust meds Dietitian: reinforce dietary advice
Urine output (UO)	Record daily urine output at home	Teach patient UO monitoring; verify reports	Interpret UO and consider diuretic use	Follow-up UO in outpatient settings	—
Urine collection for creatinine clearance	Assist with accurate 24-hour urine collection, if feasible	Instruct patient on proper urine collection method	Order urine collections for creatinine clearance	Reinforce adherence to follow-up labs	Lab: ensure timely and accurate processing
Interdialytic solute rise	Keep dialysis sessions consistent; ask about recovery	Ensure consistent predialysis lab checks; report to doctor	Evaluate solute clearance and consider dialysis taper	Coordinate care post-discharge; ensure continuity	Dialysis techs: support prelab draws
Symptoms of uremia	Report fatigue, nausea, appetite changes, or confusion	Screen for symptoms; escalate concerns	Synthesize symptoms with labs to assess clearance adequacy	Assess general well-being and symptom burden	Social work: screen for barriers to reporting symptoms
Fluid tolerance	Track weight, swelling, and BP at home	Measure and record weights and BP; report signs of overload	Determine fluid status and adjust ultrafiltration goals	Review home BP/weight and refer back if concerns arise	Dietitian: counsel on sodium and fluid restrictions
Estimated glomerular filtration rate (eGFR)	Ask about what eGFR means and if it's reliable during AKI resolution	Reinforce that eGFR is not fully reliable alone in AKI	Explain limitations of eGFR; consider multiple data points	Avoid relying solely on eGFR for medication dosing	—

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(Caution!)					

AKI, acute kidney injury; BP, blood pressure; eGFR, estimated glomerular filtration rate; PCP, primary care physician; RRT, renal replacement therapy

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Structured clinical evaluation should include assessment of volume status, BP, and medication review as well as assessment of dialysis adequacy and kidney recovery. Assessment of kidney function should occur at regular intervals, at least weekly during the first month. The WATCH-ME framework incorporates many of these elements (Table 60).[791, 1210]

Intradialytic hypotension and hemodynamic instability may delay or impair recovery of kidney function in people with AKI.[1254] There is no specific BP target for people with AKI receiving dialysis, however it may be reasonable to tolerate a slightly higher BP when there is potential for resolution to minimize the risk of renal hypoperfusion. Similarly, volume management should aim to minimize the risk of hypovolemia, intradialytic hypotension, and organ hypoperfusion, while avoiding symptomatic volume overload. Outpatients receiving RRT following AKI may experience dynamic changes in lean body mass and volume due to prolonged illness, recovery from illness, and changing kidney function, which can additionally affect dietary intake. Assessment of BP and volume (including weight) is required with each dialysis treatment. Diuretics may be helpful in managing volume and are associated with less risk of intradialytic hypotension.[761, 1255]

Medication review and management is recommended for all people transitioning to the outpatient dialysis setting following AKI. Patients and caregivers should be instructed and educated to avoid nephrotoxin exposures and be provided sick day guidance. Pharmacist-assisted medication management may reduce the risk of nephrotoxin exposure and lower rates of rehospitalization in AKI survivors.[1171, 1256] The optimal timing for initiating or resuming cardio- and renoprotective medications (e.g., ACEi, statins, SGLT2i) in adults with AKI who are still receiving RRT post hospitalization is unclear.

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Table 60 |.Post-discharge care guide for AKI-RRT patients incorporating WATCH-ME framework

Care domain (WATCH-ME)	Considerations	Recommended actions	Monitoring and follow-up	Rationale/Notes
Weight assessment (W)	• Dry weight may fluctuate • Volume status is dynamic	Educate on concept of dry weight; optimize diuretic regimens; allow permissive hypervolemia to prevent intradialytic hypotension	Regular weight checks; adjust target weight based on clinical assessment	Prevents intradialytic hypotension and supports hemodynamic stability
Access for dialysis (A)	• Central venous catheter (CVC) care • Future access planning	Educate on CVC care; promote vein preservation; discuss arteriovenous access creation or other treatment options for kidney failure if dialysis dependency continues	Monitor for signs of infection; plan for timely transition to permanent access and selection of long-term treatment modality if needed	Reduces infection risk and prepares for potential long-term dialysis needs
Teaching (T)	• Patient and caregiver understanding of AKI and dialysis process • Family education for children with AKI on RRT • Transition	Provide tailored education on AKI, dialysis procedures, medication management, and lifestyle modifications	Assess comprehension regularly; reinforce education during follow-up visits	Empowers patients and caregivers, enhancing adherence and engagement
Clearance assessment (C)	Monitoring kidney function recovery potential	Regularly assess SCr, BUN, and UO; adjust dialysis frequency and duration accordingly	Trend lab values over time; consider 24-hour urine collections for creatinine clearance, monitor urine volume at home	Facilitates timely recognition of kidney recovery and appropriate dialysis adjustments
Hypotension management (H)	Avoidance of intradialytic and postural hypotension	Set conservative ultrafiltration goals; educate on symptoms of hypotension; adjust antihypertensive medications as needed	Monitor BP pre-, intra-, and post-dialysis; review home BP logs, avoid intradialytic hypotension	Prevents renal hypoperfusion, supporting resolution and reducing cardiovascular risks
Medication management (M)	Avoidance of nephrotoxic agents; appropriate dosing	Review and reconcile medications; discontinue or adjust nephrotoxic drugs; ensure appropriate dosing for kidney function	Regular medication reviews; coordinate with pharmacists and primary care physicians	Minimizes further kidney injury and optimizes therapeutic efficacy

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Evaluation (E)	Ongoing assessment of overall health and comorbid conditions	Conduct comprehensive reviews including cardiovascular status, nutritional assessment, and psychosocial well-being	Schedule multidisciplinary follow-ups; utilize standardized assessment tools	Addresses holistic health needs, promoting overall resolution and quality of life

AKI, acute kidney injury; BP, blood pressure; BUN, blood urea nitrogen; CVC, central venous catheter; RRT, renal replacement therapy; SCr, serum creatinine; UO, urine output

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The criteria for and processes by which dialysis may be discontinued for people following AKI is covered in Chapter 5 and has not been specifically studied for people with AKI receiving outpatient dialysis. Most people with AKI who successfully discontinue dialysis in the outpatient setting will have or will be at risk for CKD. Patients should be educated about this risk, as well as the risk of recurrent AKI, and general aspects of kidney care, as outlined in Section 6.1.

Practice Point 6.4.5: Upon discontinuation of outpatient dialysis, a nephrologist should conduct a comprehensive assessment within 7 days, followed by an additional evaluation of kidney function at 90 days.

Discontinuation of dialysis represents another transition in the care and period of vulnerability for people with AKI who have been treated with RRT. Patients should be assessed by a nephrologist with the timing and frequency of follow-up determined by the person's clinical status at the time of dialysis discontinuation. While assessment should occur at a minimum of 7 days after dialysis discontinuation, volume and electrolyte disturbances may require closer and more frequent assessment. All recovering patients, regardless of the degree of resolution should have an assessment of kidney function at 90 days to assess for the presence of *de novo* or progressive CKD.

The majority of adults receiving RRT for AKI will recover sufficiently to discontinue dialysis within 90 days. People still requiring dialysis after this period of time should be reassessed with respect to prognosis. The goals of care should be discussed and agreed with the patient and caregiver, and additional patient education should be provided to inform their transition to long-term dialysis for kidney failure.

6.5. Considerations specific to children

6.5.1 Planning follow-up care for children after AKI and/or AKD

Practice Point 6.5.1.1: Assess children following AKI for global functional status at hospital discharge and for growth parameters and functional status at outpatient follow-up.

The sequelae of AKI in children can include growth restriction, functional decline, neurodevelopmental impairment, and reduced health-related quality of life,[1086, 1087, 1257-1259] in addition to hypertension and CKD. These outcomes reinforce the importance of assessments of growth parameters and functional metrics in post-AKI care of children, in addition to BP and laboratory monitoring. Post-AKI care in children requires careful interpretation of kidney function changes in the context of hemodynamic alterations. Rises in serum creatinine after initiation of RASi can reflect hemodynamic changes rather than intrinsic kidney injury and should not prompt medication discontinuation. As in adult patients, kidney function testing in children should be performed with close attention to the clinical picture and volume status.

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Follow-up plans for children after AKI may vary by age, AKI severity, duration, degree of resolution, and comorbid risk (Table 61). High-risk infants, such as those with Stage 2–3 AKI, persistent AKI (>48 hours), or residual proteinuria, require comprehensive lab evaluation, BP monitoring, and growth tracking, beginning within 3 months post-discharge. Adolescents with AKI should also receive counseling on NSAID avoidance, lifestyle risks, and reproductive health, ideally as part of transition planning. Growth parameters, including head circumference in infants, should be systematically incorporated into post-AKI follow-up given that AKI in infancy and early childhood is associated with impaired growth. Colocation of AKI follow-up assessment with other subspecialty clinics may reduce caregiver burden.

In the largest multicenter cohort to date evaluating functional outcomes after children receiving CRRT for AKI or fluid overload, functional decline was common and often persisted beyond hospital discharge.[1257] Discharge Functional Status Scale (FSS) scores were the most robust predictor of long-term outcome, highlighting the need for early, proximal assessments to trigger intervention. These findings support incorporating functional assessment tools such as the FSS, and Pediatric Quality of Life Inventory (PedsQL) into discharge planning and post-AKI surveillance. Children with elevated FSS at discharge, particularly those with sepsis, may benefit from early referral to developmental and rehabilitation services. Pediatric AKI follow-up should encompass targeted functional support and neurodevelopmental interventions, especially for high-risk populations such as preterm infants, those requiring CRRT, and survivors of septic shock.

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Table 61 |.Pediatric AKI/AKD follow-up elements stratified by age group and risk category, modified from the NICU Survivor Delphi process[288]

Age group	Risk stratification (AKI stage, duration, resolution)	Follow-up interval	Laboratory monitoring	Other monitoring
Infants (<1 yr)	Low	1–3 months	SCr, UA	BP, growth tracking
	High	1, 3, and 12 months	SCr, cystatin C, electrolytes, UA, UACR/UPCR	BP, growth tracking, kidney and bladder ultrasound if structural concern
Toddlers (1–3 yrs)	Low	1–3 months	SCr, UA	BP, growth tracking
	High	1, 3 and 12 months	SCr, cystatin C, electrolytes, UA, UACR/UPCR	BP, growth tracking, kidney and bladder ultrasound if structural concern, kidney health education, sick day guidance and kidney care for families and children
School-age (4–12 yrs)	Low	1–3 months	SCr, UA	BP, growth tracking
	High	1, 3, and 12 months	SCr, cystatin C, electrolytes UA, UACR/UPCR	BP, growth tracking, GFR estimation, AKI/CKD education, signs of HTN/CKD
Adolescents (13–18 yrs)	Low	1–3 months	SCr, UA	BP, discuss long-term risk, self-monitoring education

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	High	1, 3, and 12 months	SCr, cystatin C, electrolytes, UA, UACR/UPCR, GFR	BP, proteinuria trends, education on NSAIDs, other nephrotoxins, and CKD risk, reproductive counseling, transition planning

Low risk: Stage 1 AKI, resolved <48h, normal urinalysis (UA) & serum creatinine (SCr) at discharge from hospital; High: Stage 2–3 or AKI >48h, proteinuria or residual elevation in creatinine or cystatin C discharge, infants born <28 weeks, critical cardiac disease, BP, blood pressure; CKD, chronic kidney disease; GFR, glomerular filtration rate; HTN, hypertension; NICU, neonatal intensive care unit; NSAID, nonsteroidal anti-inflammatory drug; PCP, primary care physician; UA, urinalysis; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio

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Practice Point 6.5.1.2: In children previously taking RASi, these medications should be resumed with resolution of AKI and/or AKD, unless there is a contraindication.

The American Academy of Pediatrics recommends that children and adolescents with CKD, hypertension, and proteinuria should be treated with RASi.[1260] According to the KDIGO 2025 IgA Nephropathy and IgA Vasculitis Guideline, all children with IgA nephropathy and proteinuria >200 mg/d or UPCR >200 mg/g (>20 mg/mmol) should receive RAS blockade.[1261] RASi are also commonly indicated for pediatric cardiovascular conditions; the American Heart Association 2024 scientific statement on chronic heart failure in children and adolescents with congenital heart disease notes that RASi may be considered in children and adolescents with congenital heart disease and systemic left ventricular dysfunction, particularly in the presence of hypertension.[1262] In a 2024 randomized, double-blind trial of 375 children with heart failure due to systemic left ventricular systolic dysfunction, sacubitril/valsartan did not differ significantly from enalapril at 52 weeks using a global rank endpoint (Mann–Whitney probability 0.52; p=0.42), with both arms demonstrating improvements in functional status and biomarkers and similar safety profiles.[1263] Temporary discontinuation of RASi during episodes of AKI and/or AKD in these pediatric populations and others where the benefit from RASi may exist should not preclude resumption once clinical stability is achieved. As in adults, careful clinical assessment and laboratory monitoring are essential to ensure safe reintroduction and to avoid missed opportunities for long-term organ protection.

6.5.2. Post-discharge care for children receiving RRT following AKI in the outpatient setting

Practice Point 6.5.2.1: A risk-based approach guided by cause and severity of AKI and kidney health assessments at hospital discharge and one year following an AKI episode can be used to determine need for future nephrology follow-up in children.

A limited pediatric nephrology workforce and disparities in access to specialized care can adversely impact the delivery of care for children following AKI. A tiered follow-up framework informed by AKI severity and the context and cause of the AKI episode, with nephrology referral and surveillance for children with Stage 2–3 AKI, delayed kidney recovery, or predisposing conditions such as congenital anomalies of the kidney and urinary tract or other primary kidney diseases has been proposed.[288] A prospective study showed that children who demonstrate normal kidney function in the first year following an episode of AKI were at low risk of developing CKD within the subsequent 2–4 years.[1264] The risk of CKD was lowest when preserved eGFR was combined with absence of proteinuria and hypertension. These findings support a risk-based approach to post-AKI follow-up in which children with a normal kidney health assessment at one year without complex comorbidities or subsequent AKI episodes may be safely discharged from pediatric nephrology care, allowing for more efficient allocation of resources and tailored long-term surveillance (Table 62)

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Table 62 |.Sample risk assessment approach for pediatric AKI/AKD survivors, modified from the NICU Survivor Delphi process[288]

Risk category	AKI severity	Kidney status at discharge	Risk factors	Hospital course	Outcomes	Suggested follow-up
Low risk	Stage 1, duration <48 h	Normal SCr and UA	None or mild comorbidities	No ICU admission, short hospital stay, no RRT	Full resolution likely; low risk of CKD	Routine monitoring with pediatrician
High risk	Stage 2–3, duration >48 h, or RRT requirement	Residual elevation in SCr or cystatin C, or proteinuria	•Infants born <28 weeks •Critical cardiac disease •Non-kidney organ transplant •Cancer	• ICU admission • Prolonged hospital stay • Mechanical ventilation • Exposure to nephrotoxic medication • RRT use	Increased risk of AKD, CKD, and mortality	Structured nephrology follow-up, potentially delayed discharge from kidney clinic
High risk	Primary kidney disease		•Glomerulonephritis •Tubular-interstitial nephritis •Vasculitides •CAKUT		Increased risk of AKD CKD	Longterm nephrology follow-up

AKD, acute kidney disease; AKI, acute kidney injury; CAKUT, congenital anomalies of the kidney and urinary tract; CKD, chronic kidney disease; ICU, intensive care unit; RRT, renal replacement therapy; SCr, serum creatinine; UA, urinalysis

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Practice Point 6.5.2.2: Children recovering from AKI treated with RRT require individualized follow-up that includes age-appropriate functional and developmental assessments, growth and neurodevelopmental surveillance, and integrated care across nephrology, primary care, and relevant subspecialties.

There is evidence of a rising incidence of pediatric AKI requiring RRT, with population-based data from Canada showing an increase from 0.58 to 0.65 per 1,000 person-years between 1996 and 2015.[1109] Over this period, there has been a notable shift in modality use: the relative use of PD has declined, while both intermittent hemodialysis and CRRT have increased.[1109, 1218] These trends likely reflect both increased illness severity and broader access to advanced extracorporeal technologies. Among survivors of AKI treated with RRT, up to 70% exhibit subclinical evidence of kidney damage, such as proteinuria, hypertension, and reduced eGFR after dialysis is discontinued.[1017] This underscores the importance of structured, longitudinal follow-up that includes regular assessment of BP and kidney function.

The majority of children who survive after RRT for AKI, recover kidney function, but rates vary by illness severity, modality, and underlying condition.[1265] In an international, multicenter cohort study of critically ill children treated with CRRT, 9.4% remained dialysis-dependent at 90 days.[1088] Resolution typically occurs within 2–6 weeks after AKI onset, but delayed or incomplete resolution is more common in children with multisystem organ dysfunction, preexisting CKD, onco-hematologic conditions, or significant nephrotoxin exposure. The EurAKId registry, a prospective European cohort, found that 10%–30% of children treated with RRT for AKI experienced delayed resolution or transitioned to dialysis dependence, especially in high-risk subgroups.[1038]

Recovery of kidney function after RRT may also occur in the outpatient setting. A retrospective analysis of the United States Renal Data System showed that resolution was more frequent among younger children, females, non-White patients, and those initially treated with hemodialysis.[1266] Children with acute tubular necrosis had the highest resolution rates (17.5%), reinforcing the importance of tailoring expectations and follow-up intensity based on the underlying etiology of AKI. These data support cautious use of the kidney failure label in children with potentially reversible causes of kidney injury, emphasizing the need for vigilant surveillance of residual kidney function over time.

Optimal care for children recovering from AKI treated with RRT should include comprehensive clinical and laboratory assessment of kidney recovery, regular medication review and reconciliation with attention to nephrotoxic exposures, and patient and caregiver education on recognizing signs of resolution or deterioration. Nutritional and fluid management goals must account for growth and developmental changes, with dynamic

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adjustments throughout resolution. Care models should facilitate coordination between intensive care, pediatric nephrology, primary care, and rehabilitation services to address the complex needs of these children. Given the limited pediatric nephrology workforce and potential barriers to specialty care, centralized or telehealth-enabled follow-up could be considered. Additionally, educating general pediatricians and relevant subspecialists on post-AKI surveillance and criteria for nephrology referral can enhance the safety and continuity of care during the vulnerable resolution phase.

Pediatric survivors of AKI or early-onset CKD who progress to kidney failure in childhood and adolescence experience enduring disruptions in social, emotional, and functional domains during young adulthood. While many adapt to chronic illness, the cumulative burden of kidney injury early in life, including developmental impacts, treatment intensity, and transplant challenges, manifests in constrained life participation. Tracking employment, independence, and health-related quality of life metrics into adulthood are also essential aspects of pediatric AKI follow-up.[1267]

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METHODS FOR GUIDELINE DEVELOPMENT

Aim

The aim of this project was to update the *KDIGO 2012 Clinical Practice Guideline for Acute Kidney Injury*.[608] The guideline update development methods are described below.

Overview of process

These guidelines adhered to international best practices for guideline development (Appendix B: Supplementary Tables S2, S3, and S4),[1268, 1269] and have been reported in accordance with the Institute of Medicine and Appraisal of Guidelines for Research and Evaluation (AGREE) II reporting checklists.[1270] The processes undertaken for the development of the *KDIGO 2026 Clinical Practice Guideline for Acute Kidney Injury (AKI) and Acute Kidney Disease (AKD)* are described below.

- Appointing Work Group members and the Evidence Review Team (ERT)
- Defining scope and the topics of interest for the guideline
- Developing and refining topics for systematic evidence review
- Developing and implementing literature search strategies
- Selecting studies according to predefined eligibility criteria
- Conducting data extraction and risk of bias assessment of the included studies
- Conducting evidence syntheses and meta-analysis, where appropriate
- Assessing the certainty of evidence for each outcome across studies, and assessing the overall certainty of evidence across critical outcomes
- Finalizing guideline recommendations, practice points, and supporting rationale
- Grading the strength of recommendations, based on the overall certainty of evidence and other considerations
- Convening a public review of the guideline draft in March 2026
- Amending the guideline based on the external review feedback and updated systematic reviews
- Finalizing and publishing the guideline

Commissioning of Work Group and ERT for the guideline update

For the guideline update, KDIGO and the Co-Chairs assembled and engaged a Work Group with expertise in adult and pediatric nephrology, critical care medicine, emergency medicine, general medicine, pharmacy and pharmacology, as well as people with lived experience of AKI. The Brown University Center for Evidence Synthesis in Health in Providence, Rhode Island which has expertise in nephrology, evidence synthesis, and guideline development was contracted as the ERT and was tasked with conducting and

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updating the systematic reviews. The ERT coordinated the methodological and analytical processes of guideline development, including literature searching, data extraction, risk of bias assessment, evidence synthesis and meta-analysis, grading the certainty of the evidence for each critical and important outcome, and grading the overall certainty of the evidence for the recommendations. KDIGO Methods Committee representatives also ensured the guideline development process adhered to the KDIGO methods as outlined in the KDIGO Methods Manual and provided guidance of guideline methodology throughout the development of the guideline. The Work Group was responsible for defining the scope of the guideline, writing the recommendations and the underlying supporting text, grading the strength of the recommendations, and developing practice points.

Defining scope and formulating key clinical questions

The KDIGO 2012 AKI Guideline was reviewed by the Co-Chairs to establish a framework for the 2026 update. A complete Scope of Work encompassing both legacy topics and newly identified clinical topics for inclusion in the update was revised and finalized based on feedback from the Work Group and external review. Based on this list of topics, the ERT suggested topics for systematic evidence review to inform the development of evidence-based recommendations. In an iterative process, with additional discussion with Work Group members, the list of systematic review topics was finalized, and study eligibility criteria were determined based on the Population, Intervention, Comparator, Outcomes, and Study design (PICOS) formulation. A shortlist of potential outcomes of interest was derived from a 2019 National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) workshop,[1161] a core outcome set for multimorbidity research,[1271] and the ERT experience with kidney guidelines. Outcome prioritization was based on consideration of the Standardized Outcomes in Nephrology (SONG) outcome sets (https://songinitiative.org/); although SONG has not published an outcome set specific to AKI.

Details of the PICOS questions are provided with prioritized outcomes noted in Table 63. For all topics, relevant existing systematic reviews of eligible primary studies were also identified. All evidence reviews were conducted in accordance with the Cochrane Handbook,[1272] the Agency for Healthcare Research and Quality Evidence-based Practice Center Program Methods Guide,[1273] and guideline development adhered to the standards of GRADE.[1274]

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Table 63 | Clinical questions and systematic review topics in PICOS format

Research questions (RQ)	Population	Intervention/ predictor	Comparator	Outcomes[a]	Study design[b]
Chapter 1. AKI and AKD definition, identification, and classification					
RQ 1: For patients being evaluated for or with established AKI, how do different components of the KDIGO AKI definition, and variants thereof, compare in their association with AKI outcomes?	• People at risk for AKI • People with established AKI • In-patient, having a procedure, being evaluated for possible AKI, or with AKI	• KDIGO AKI definition (SCr, UO), full, components, and combinations, including variants of these, including variant definitions of stages • Methods to estimate baseline SCr • *Exclude* o *Evaluation of factors as continuous variables* o *Evaluation of measures other than SCr or UO*	• Alternative thresholds, etc. • Alternative methods to estimate baseline SCr • *Exclude* o *Comparison with RIFLE or AKIN criteria (except pediatric RIFLE)* o *Comparison of AKI stages*	• **Death, all-cause** • **Death, kidney-related** • **AKI stages (incident), including any stage (≥Stage 1)** • **AKI requiring RRT** • **MAKE (at ≥90 days)** • CKD G3-G5 (at ≥90 days) • CKD G5D (dialysis) (at ≥90 days)	• Direct comparisons of different thresholds/ definitions • Categorical factors (e.g., predictors) • Diagnostic test analysis (e.g., test accuracy) • N≥1000
RQ 2: What is the association between AKI (<7 days) or AKD (7-90 days) trajectories and AKI and CKD (>90 days) outcomes?	• Hospital general or ICU population with established AKI or AKD, defined by KDIGO, RIFLE, AKIN (or variants) • *Exclude* o *Specific hospital populations (e.g., surgical patients only, sepsis, trauma, malaria, preterm neonates)* o *Ad hoc, claims-based, or unclear definition of AKI or AKD*	• Specified definitions of AKI or AKD trajectory o *Transient AKI* o *Persistent AKI* o *Progressive or worsening AKI or AKD* o *Recurrent AKI* o *Recovered AKI or recovered AKD* o *Other similar concepts*	• Alternative trajectory	• **Death, all-cause** • **Death, kidney-related** • **AKI stages (incident), including any stage (≥Stage 1)** • **AKI requiring RRT** • **MAKE (at ≥90 days)** • CKD G3-G5 (at ≥90 days) • CKD G5D (dialysis) (at ≥90 days) • ICU admission • Hospital or ICU length of stay	• Direct comparisons of different thresholds/ definitions • Categorical factors (e.g., predictors) • Diagnostic test analysis (e.g., test accuracy) • N≥1000 adults or ≥500 non-infant children or ≥100 infants

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Research questions (RQ)	Population	Intervention/ predictor	Comparator	Outcomes[a]	Study design[b]
RQ 3: What is the prognosis of patients diagnosed with AKD?	● People with AKD ● *Exclude* ○ *Ad hoc, claims-based, or unclear definition of AKI or AKD*	● AKD diagnosis (with our without known prior AKI), defined by KDIGO, RIFLE, AKIN (or variants)	● Recovery from AKI (without AKD) ● None (no comparator necessary)	● **Death, all-cause** ● **AKD requiring RRT** ● **MAKE (at ≥90 days)** ● Complete recovery ● CKD G3-G5 (at ≥90 days) ● **CKD G5D (dialysis) (at ≥90 days)**	● Comparative or single group ● *Exclude* ○ *Case control study* ● Published since 2013 ● N≥1000 adults or ≥100 children
Chapter 2. AKI prediction, risk stratification, and diagnostic evaluation					
RQ 4: For patients being evaluated for or with established AKI, what is the (comparative) test accuracy of or association between specific predictors or diagnostic tests and AKI outcomes?	● People at risk for AKI ● People with established AKI	a) Clinical risk scores b) Clinical decision support systems, including alerts, NINJA, sniffers, detectors c) Specified prediction models d) Furosemide stress test e) Kinetic eGFR f) Urine microscopy markers of acute tubular necrosis g) Biomarkers (i) Clusterin (ii) Cystatin-C (iii) KIM-1 (iv) NAG (v) NGAL (vi) Osteopontin (vii) TIMP2 x IGFBP7 (viii)Proenkephalin (ix) L-FABP (x) CCL-14 h) Biopsy/histology features i) Kidney imaging (i) Ultrasound (ii) MRI	● Alternate finding ● Alternate test	● **Death** ● **AKI, any stage (incident) (at risk population)** ● **AKI, stage 3 (incident)** ● **AKI requiring RRT** ● **MAKE (at ≥90 days)** ● Diagnostic test accuracy ● Duration of AKI ● CKD G3-G5 (at ≥90 days) ● CKD G5D (dialysis) (at ≥90 days)	● Multivariable-adjusted, longitudinal studies ● Direct comparisons of different thresholds/definitions, with adjustment ● Diagnostic test analysis (e.g., test accuracy), with or without adjustment ● For biomarkers: existing SRs only

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Research questions (RQ)	Population	Intervention/ predictor	Comparator	Outcomes[a]	Study design[b]
RQ 5: For patients being evaluated for or with established AKI, what are the clinical effects of using/implementing specific predictors or diagnostic tests on subsequent AKI outcomes?	● People at risk for AKI ● People with established AKI	● Use of tool or test listed in RQ 4	● Not using tool or test ● Alterative tool or test	● **Death** ● **AKI, any stage (incident) (at risk population)** ● **AKI, stage 3 (incident)** ● **AKI requiring RRT** ● **MAKE (at ≥90 days)** ● Duration of AKI ● CKD G3-G5 (at ≥90 days) ● CKD G5D (dialysis) (at ≥90 days)	● RCT
Chapter 3. Prevention and treatment of AKI					
RQ 6: For patients at risk for developing AKI, what are the effects of fluid management strategies to prevent AKI?	● People at increased risk for AKI ○ Inpatient	● Crystalloids ○ Balanced crystalloids vs. other crystalloids ○ Crystalloids vs. synthetic colloids ○ Crystalloids vs. albumin ● Fluid amount: More vs. less ● Oral vs. i.v. rehydration ● Protocolized hemodynamic therapy ● Vasopressors incorporated in a fluid protocol ● Mean arterial pressure targets ● AKI care bundle	● Alternative strategy, including "usual care"	● **Death, all-cause** ● **AKI, any stage (incident)** ● **AKI, stage 3 (incident)** ● **AKI requiring RRT** ● **MAKE (at ≥90 days)** ● Duration of AKI ● CKD G3-G5 (at ≥90 days) ● CKD G5D (dialysis) (at ≥90 days) ● **Serious adverse events** (Stage ≥3) ○ Fluid overload or heart failure	● RCT ● For comparison of crystalloids and other fluids: existing SRs or network meta-analyses only
RQ 7: For patients undergoing cardiac surgery, what are the effects of prophylactic i.v. amino acids on AKI outcomes?	● People undergoing cardiac surgery (at increased risk for AKI)	● Intravenous (i.v.) amino acids	● No i.v. amino acids	● **AKI, any stage (incident)** ● AKI, stage 3 (incident) ● **AKI requiring RRT** ● **MAKE (at ≥90 days)** ● Duration of AKI ● **Serious adverse events (Stage ≥3)** ● **Discontinuation due to AE**	● RCT

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Research questions (RQ)	Population	Intervention/ predictor	Comparator	Outcomes[a]	Study design[b]
RQ 8: For patients undergoing cardiac surgery, who do not receive propofol anesthetic, what are the effects of remote ischemic preconditioning on AKI-related outcomes and serious treatment-related adverse effects?	● Patients undergoing cardiac surgery ● *Exclude* ○ *Received propofol anesthesia*	● Remote ischemic preconditioning as part of anesthesia or preoperative protocol	● No remote ischemic preconditioning	● **Death** ● **AKI, any stage (incident)** ● **AKI requiring RRT** ● **MAKE (at ≥90 days)** ● Hospital duration ● **Serious adverse events (Stage ≥3)**	● RCT
RQ 9: For patients at risk of and with established AKI, what are the effects of alert (vs. no alert) on AKI outcomes?	● Patients identified with elevated SCr ○ Inpatient *or outpatient*	● Automated alert (by EHR system)	● No alert	● **AKI, any stage (incident)** ● AKI, stage 3 (incident) ● **AKI requiring RRT** ● **MAKE (at ≥90 days)** ● Duration of AKI ● Intensive care admission, unplanned	● RCT
RQ 10: For people with AKI with hypervolemia, with or without cardiorenal syndrome, what are the effects of different fluid removal approaches on AKI outcomes?	● People with AKI with hypervolemia ○ Inpatient	● Extracorporeal (isolated ultrafiltration, CRRT, IHD) vs. diuretics (any) ● Continuous vs. intermittent diuretics ● Furosemide (alone) vs. furosemide + other diuretic (combination)	● Alternative intervention	● Death ● **AKI requiring RRT** ● **MAKE (at ≥90 days)** ● **Duration of AKI** ● CKD G3-G5 (at ≥90 days) ● **CKD G5D (dialysis) (at ≥90 days)** ● **Serious adverse events (Stage ≥3)**	● RCT
RQ 11: For patients with HRS, what is the effect of vasoactive agents on AKI outcomes?	● People with hepatorenal syndrome	● Terlipressin ● Midodrine + octreotide ● Norepinephrine	● No vasoactive agent ● Alternative vasoactive agent	● **Death** ● **Reversal of HRS** ● **AKI requiring RRT** ● **MAKE (at ≥90 days)** ● Duration of AKI ● Quality of life ● **Serious adverse events (Stage ≥3)** ● **Discontinuation due to AE**	● RCT

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Research questions (RQ)	Population	Intervention/ predictor	Comparator	Outcomes[a]	Study design[b]
RQ 12: For patients critically ill with acidosis, with or without AKI, what are the effects of i.v. bicarbonate on AKI outcomes?	● People critically ill with acidosis, with or without AKI	● Intravenous bicarbonate	● No i.v. bicarbonate	● **Death** ● **AKI, stage 3 (incident)** ● **AKI requiring RRT** ● **MAKE (at ≥90 days)** ● Hospital duration ● **Serious adverse events (Stage ≥3)** ● **Discontinuation due to AE**	● RCT
RQ 13: For patients with, or at risk for, TLS, rhabdomyolysis, or pigment nephropathy, what are the effects and comparative effects of specified treatments on AKI outcomes?	● People with or at risk for o TLS, including with myeloma o Rhabdomyolysis o Pigment nephropathy	● Fluid strategies (for all conditions) ● Allopurinol (for TLS) ● Rasburicase (for TLS) ● Febuxostat (for TLS) ● Bicarbonate (urine alkalinization) (for all conditions) ● Dialysis or ultrafiltration (for all conditions)	● No listed intervention ● Alternative listed intervention	● **Death** ● **Resolution of TLS, rhabdomyolysis, pigment nephropathy** ● **AKI, stage 3 (incident)** ● **AKI requiring RRT** ● **MAKE (at ≥90 days)** ● Duration of AKI ● CKD G3-G5 (at ≥90 days) ● **CKD G5D (dialysis) (at ≥90 days)** ● **Serious adverse events (Stage ≥3)** o **Discontinuation due to AE** o Rash (allopurinol) o Stevens Johnson syndrome (allopurinol) o Toxic epidermal necrolysis (allopurinol) ● Cytopenia (allopurinol)	● RCT
RQ 14: For neonates with neonatal asphyxia, what are the effects of theophylline on AKI outcomes?	● Neonates with AKI o Inpatient	● Theophylline	● No theophylline	● **Death** ● **AKI, stage 3 (incident)** ● **AKI requiring RRT** ● **MAKE (at ≥90 days)** ● Hospital duration ● **Serious adverse events (Stage ≥3)** ● **Discontinuation due to AE**	● RCT ● Nonrandomized comparative studies, prospective or retrospective

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Research questions (RQ)	Population	Intervention/ predictor	Comparator	Outcomes[a]	Study design[b]
RQ 15: For children undergoing cardiopulmonary bypass, what are the effects of intraoperative nitric oxide on AKI outcomes?	● Children undergoing cardiopulmonary bypass	● Nitric oxide, inhaled or infused	● No nitric oxide	● **Death** ● **AKI, stage 3 (incident)** ● **AKI requiring RRT** ● **MAKE (at ≥90 days)** ● Hospital duration ● **Serious adverse events (Stage ≥3)** ● **Discontinuation due to AE**	● RCT ● Nonrandomized comparative studies, prospective or retrospective
RQ 16: For children with malaria, what are the effects of acetaminophen/paracetamol on AKI outcomes?	● Children with malaria (with or without AKI)	● Acetaminophen/ paracetamol ● Other antipyretic	● No acetaminophen ● Other antipyretic (strategy)	● **Death** ● **AKI, any stage (incident)** ● **AKI requiring RRT** ● **MAKE (at ≥90 days)** ● Hospital duration ● **Serious adverse events (Stage ≥3)** ● **Discontinuation due to AE**	● RCT ● Nonrandomized comparative studies, prospective or retrospective
Chapter 4. Drug and nephrotoxin-associated AKI					

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Research questions (RQ)	Population	Intervention/ predictor	Comparator	Outcomes[a]	Study design[b]
RQ 17: For patients with or at risk for AKI who are on medications that put them at risk for nephrotoxic injury, what are the effects and comparative effects of drug stewardship strategies?	● People at increased risk for AKI on medications that put them at risk for nephrotoxic injury ● People with established AKI who are on medications that put them at risk for nephrotoxic injury ○ In hospital or Emergency Department ● *Exclude* ○ Receiving RRT	● Multimodal stewardship ○ Therapeutic drug monitoring of ▪ Antimicrobials ▪ Calcineurin inhibitors ○ Drug monitoring ▪ Drug-drug interactions ▪ Nephrotoxic burden surveillance ▪ Clinical decision support systems ▪ Via EHR ○ Kidney function monitoring (intensive, increased vigilance, proactive) ● Pharmacist oversight (in the ICU) ● Different dosing regimens (continuous, intermittent, extended, daily) for ○ Aminoglycosides ○ Vancomycin ○ Beta lactams	● No drug stewardship strategy ● Alternative strategy	● **Death, all-cause** ● **Death, drug-purpose related (e.g., due to infection with aminoglycoside dosing regimen)** ● **AKI, any stage (incident)** ● **AKI requiring RRT** ● **MAKE (at ≥90 days)** ● Duration of AKI`	● RCT ● Nonrandomized comparative studies with multivariable adjustment or matching, prospective or retrospective
RQ 18: For patients undergoing medical or surgical procedures, or with acute illnesses who are at increased risk of AKI, what is the effect of temporary cessation of medications on AKI outcomes?	● People at increased risk for AKI due to ○ Relevant medical or surgical procedures ○ Acute illness ● Any setting	● Discontinuation of ○ RASi ○ Diuretics ○ SGLT2i ○ NSAIDs (specific to surgical patients) ○ Finerenone ○ GLP-1 agonists	● Continue medication	● **Death, all-cause** ● AKI, any stage (incident) ● **AKI, stage 3 (incident)** ● **AKI requiring RRT** ● **MAKE (at ≥90 days)** ● Duration of AKI ● Hospital admission, unplanned ● **Poor control of underlying condition** (e.g., hypertension, heart failure, diabetes)	● RCT

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Research questions (RQ)	Population	Intervention/ predictor	Comparator	Outcomes[a]	Study design[b]
RQ 19: For people undergoing imaging with intravascular iodinated contrast agents, what are the factors that increase the risk of AKI after contrast?	● People receiving intravascular (i.v., intra-arterial) iodinated contrast agents	● Risk scores ● Specific, independent, patient characteristics, including past medical history ● Specific, independent settings, conditions, scenarios	● Alternate	● **AKI, any stage (incident)** ● Duration of AKI	● Diagnostic test analysis, for scores ● Multivariable-adjusted, longitudinal studies for independent predictors ● N≥1000 adults or ≥100 children
RQ 20: For people undergoing imaging with intravascular iodinated contrast agents, what are the effects of hydration vs no hydration?	● People receiving intravascular (i.v., intra-arterial) iodinated contrast agents	● Hydration (i.v. or oral)	● No hydration	● **AKI, any stage (incident)** ● Duration of AKI	● RCT
Chapter 5. Renal replacement therapy					
RQ 21: For patients with AKI who require RRT, what are the comparative effects of early versus standard (late) versus delayed initiation of RRT on AKI outcomes?	● People with AKI who require (or are about to require) RRT	● Early initiation of RRT ● Delayed initiation of RRT	● Standard ("late") initiation of RRT	● **Death, all-cause** ● **Time on RRT** ● Complete recovery ● Length of hospital stay ● Length of ICU stay ● CKD G3-G5 (at ≥90 days) ● **CKD G5D (dialysis) (at ≥90 days)** ● **Serious adverse events** (Stage ≥3) o Electrolyte disorders o Hemodynamic instability o Hypophosphatemia o Complications from line insertion o Bleeding o Encephalopathy	● RCT

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Research questions (RQ)	Population	Intervention/ predictor	Comparator	Outcomes[a]	Study design[b]
RQ 22: For patients with AKI who require RRT, what are the comparative effects of different RRT modalities on AKI outcomes?	● People with AKI who require (or are about to require) RRT	● Continuous RRT (CRRT) ● Intermittent hemodialysis o Short intermittent o Prolonged intermittent RRT o Sustained low efficiency dialysis (SLED) ● Acute peritoneal dialysis	● Alternative modality or variant	● **Death, all-cause** ● **Time on RRT** ● Complete recovery ● Length of hospital stay ● Length of ICU stay ● CKD G3-G5 (at ≥90 days) ● **CKD G5D (dialysis) (at ≥90 days)** ● **Serious adverse events** (Stage ≥3) o Electrolyte disorders o Hemodynamic instability o Hypophosphatemia o Complications from line insertion o Bleeding o Encephalopathy	● RCT
RQ 23: For patients with AKI undergoing RRT, what are the comparative effects of different RRT dosing regimens or prescriptions for small solute clearance on AKI outcomes?	● People with AKI who require RRT	● Different starting doses ● Based on urea reduction ratio (URR) ● Based on Kt/V (including weekly) ● Based on replacement fluid / effluent volume	● Alternative starting dose ● Alternative dose or prescription	● **Death, all-cause** ● **Time on RRT** ● Complete recovery ● Length of hospital stay ● Length of ICU stay ● CKD G3-G5 (at ≥90 days) ● **CKD G5D (dialysis) (at ≥90 days)** ● **Serious adverse events** (Stage ≥3) o Electrolyte disorders o Hemodynamic instability o Hypophosphatemia o Complications from line insertion o Bleeding o Encephalopathy	● RCT

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Research questions (RQ)	Population	Intervention/ predictor	Comparator	Outcomes[a]	Study design[b]
RQ 24: For patients with AKI undergoing CRRT, what are the comparative effects of different anticoagulation approaches on AKI outcomes?	● People with AKI who require RRT	● Anticoagulation (vs. no anticoagulation) ● Regional citrate anticoagulation ● Unfractionated heparin ● Low molecular weight heparin ● Direct thrombin inhibitors ● Factor Xa inhibitors ● Prostacyclin / Epoprostenol ● Argatroban ● Nafamostat ● Defined anticoagulation protocols	● Alternative intervention	● **Clotting** ● **Serious adverse events** (Stage ≥3) ○ **Discontinuation due to AE** ○ **Bleed** ○ **Stroke**	● RCT
Chapter 6. Follow-up care after AKI and/or AKD					

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Research questions (RQ)	Population	Intervention/ predictor	Comparator	Outcomes[a]	Study design[b]
RQ 25: For patients who have survived an episode of AKI ("post-AKI"), what are the effects or comparative effects of different care models or interventions on health and resource-use outcomes?	● People are post-AKI (after an episode of AKI) ● People with AKD post-AKI ○ Outpatient	● Specified care models ● Specified groups of providers ● Transition of care models	● Alternative approach	● Process measures of CKD care ○ Implementation of recommended care processes ○ Restarting of medication of prognostic benefit ○ Medication adherence ● Immediate/Intermediate clinical outcomes ○ Hospital readmission ○ **Recurrent AKI** ○ Hypertension ○ Volume overload ● Longer term clinical outcomes ○ **CKD G3-G5 (at ≥90 days)** ○ **CKD G5D (dialysis) (at ≥90 days)** ○ **Death, all-cause** ○ Major Adverse Cardiovascular events (MACE) ● Other health and care resource use ○ ED visits ○ Hospital visits ○ Primary care visits ○ Social care costs ● Person-centered outcomes ○ **Health-related Quality of Life** ○ Health status ○ Symptom Burden ○ Psychological Burden (anxiety, depression, social isolation) ○ Treatment Burden ○ Patient experience ○ Self-management ○ Loneliness	● RCT ● Multivariable-adjusted, longitudinal studies for independent predictors

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Research questions (RQ)	Population	Intervention/ predictor	Comparator	Outcomes[a]	Study design[b]
RQ 26: For patients who have survived an episode of AKI ("post-AKI"), what are the effects of resuming (vs. not resuming) medications on clinical outcomes?	● People are post-AKI (after an episode of AKI) ● People with AKD post-AKI ○ Outpatient	● Resumption of ○ RASi ○ NSAIDs ○ Finerenone ○ GLP-1 agonists	● Not resuming medications	● **Death, all-cause** ● **Recurrent AKI episode** ● MAKE (at ≥90 days) ● **Poor control of underlying condition (e.g., hypertension, heart failure, diabetes)** ● CKD G3-G5 (at ≥90 days) ● CKD G5D (dialysis) (at ≥90 days) ● Quality of life ● **Serious adverse events (Stage ≥3)** ● **Discontinuation due to AE**	● RCT ● Multivariable-adjusted, longitudinal studies for independent predictors

[a]Bold outcomes are critical; un-bolded outcomes are important.[111] [b]For all topics, relevant existing systematic reviews of eligible primary studies were also identified. AE, adverse events; AKD, acute kidney disease; AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; CCL-14, C-C motif chemokine ligand 14; CKD G3-G5, CKG grade 3 to 5; CKD G5D, chronic dialysis; CKD, chronic kidney disease; CRRT, continuous renal replacement therapy; EHR, electronic health record; GLP-1 agonists, glucagon-like peptide-1 receptor agonists; HRS, hepatorenal syndrome; i.v., intravenous; ICU, intensive care unit; IHD, intermittent hemodialysis; KDIGO, Kidney Disease: Improving Global Outcomes; KIM-1, kidney injury molecule-1; L-FABP, liver fatty acid binding protein; MRI, magnetic resonance imaging; NAG, N acetyl-beta-D-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin; NINJA, Nephrotoxic Injury Negated by Just-in time Action; NSAIDs, nonsteroid anti-inflammatory drugs; PICOS, Population, Intervention, Comparator, Outcomes, and Study design; RASi, renin-angiotensin system inhibitors; RCT, randomized controlled trial; RIFLE, Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease; RQ, Research Question; RRT, renal replacement therapy; SCr, serum creatinine; SGLT2i, sodium-glucose cotransporter-2 inhibitors; SR, systematic review; TIMP2xIGFBP7, tissue inhibitor of metalloproteinases-2 and insulin-like growth factor-binding protein 7; TLS, tumor-lysis syndrome; UO, urine output.

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Literature search and article selection

Searches were conducted in MEDLINE (via PubMed) and Embase from 2013 (after publication of the KDIGO 2012 AKI Guideline) through January to June 2025, on a rolling basis, with an update during public review in March/April 2026. The search strategies for all databases are provided in Appendix A: Supplementary Tables S1. Throughout the systematic review and guideline development process, additional studies suggested by the Work Group were assessed for eligibility and incorporated as appropriate.

The unique titles and abstracts resulting from the searches were screened in duplicate by members of the ERT, using the web-based screening tools SRDRplus or the VADRR platform (https://vadrr.org/), which use large language models to sort abstracts based on likely relevance. To simplify the screening process, topics were batched by similarity and reviewed in batches. Once the team established a shared consensus through initial group reviews, the remaining abstracts were screened in duplicate, with adjudication of conflicts by the whole team. The process for each batch ended either when the batch was fully screened or when 400 consecutive abstracts were rejected suggesting a <1% chance of finding more relevant studies. All potentially relevant studies were retrieved in full text and rescreened in duplicate, with full team adjudication of conflicts.

For topics with high quality existing systematic reviews, the ERT sought additional eligible primary studies published subsequent to the review in most cases and also included other eligible studies found to have been omitted by the reviews. As noted in Table 63, existing systematic reviews of biomarkers used to predict AKI (RQ 4) or comparisons of intravenous fluids (RQ 6) were not updated.

The search identified 34,835 individual citations (Figure 23), if which1174 were identified for full-text screening, plus an additional 79 additional records suggested by Work Group members or found in reference lists of existing systematic reviews or guidelines. Ultimately, 355 studies, including both primary studies and systematic reviews, were included. These include 72 for Chapter 1, 59 for Chapter 2, 108 for Chapter 3, 57 for Chapter 4, 37 for Chapter 5, and 22 for Chapter 6.

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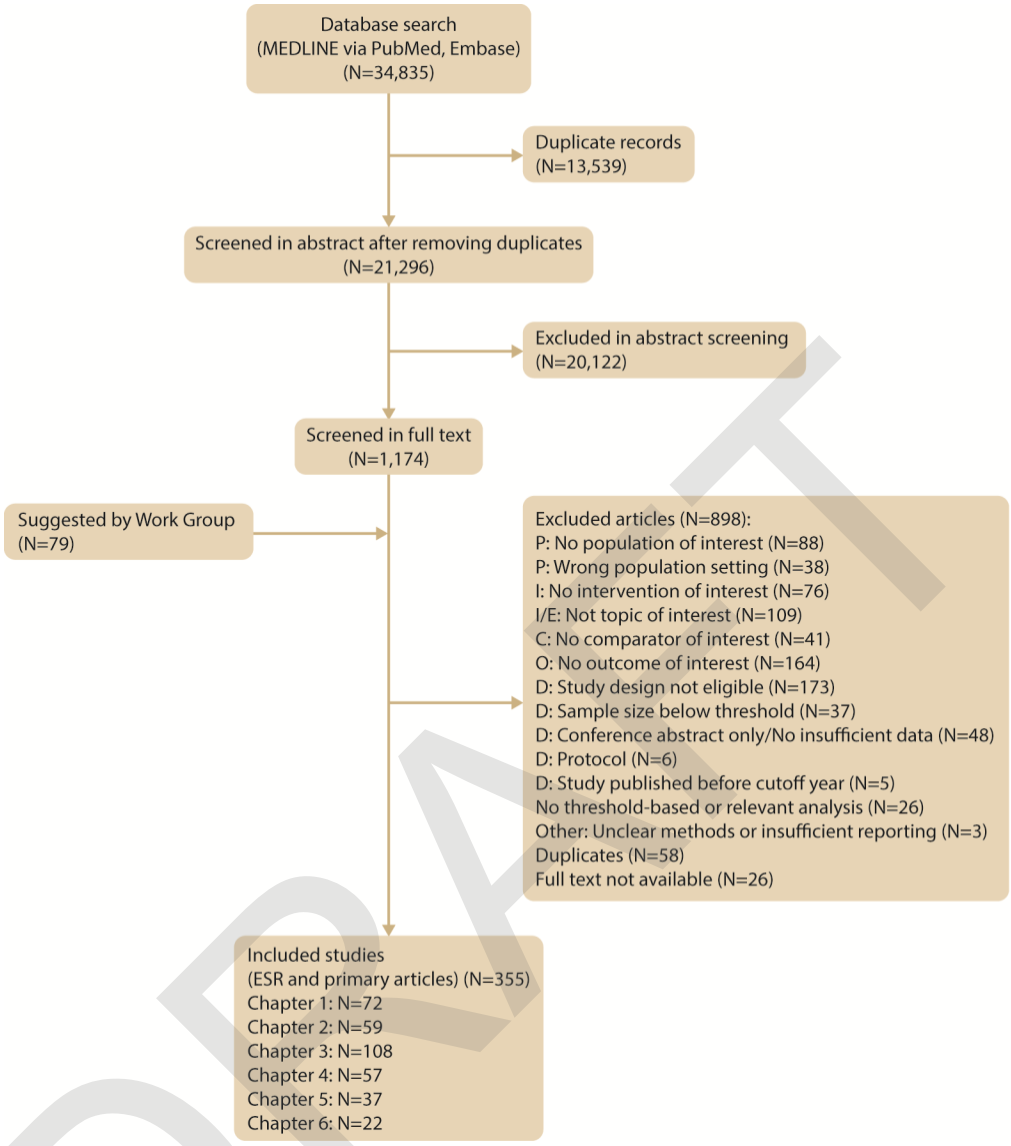

Figure 23 | Search yield and study flow diagram. C, comparator; D, study design; E, exposure(s); ESR, existing systematic review; I, intervention(s); O, outcome(s); P, population

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Data extraction

Data extraction, from primary studies and existing systematic reviews, was performed by one ERT member and confirmed by a second member of the ERT. Any differences among members of the ERT were resolved through discussion. A third reviewer was included if consensus could not be achieved. For some topics with existing systematic reviews that did not provide sufficiently complete reporting of study descriptions or results data or did not evaluate prioritized outcomes that were likely to have been reported, the ERT sought the primary studies and extracted from these.

Risk of bias of studies

Studies were assessed for risk of bias and methodological concerns. The ERT used the Cochrane Risk of Bias tool to evaluate risk of bias for RCTs[1275] based on the risk of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential biases.

For nonrandomized, observational comparative studies of interventions, pertinent questions from the Cochrane Risk of Bias tool pertaining to outcome assessor blinding, incomplete outcome data, and selective reporting were used as were selected questions from the Risk Of Bias In Non-Randomized Studies - of Interventions (ROBINS-I) tool.[1276] Specifically, comparative studies were evaluated as to whether evaluated cohorts were comparable and whether potential confounders were accounted for.

For all intervention studies, including single group studies, it was determined whether analyses were intention-to-treat were per-protocol, whether selection of participants into the study was based on participant characteristics observed after the start of intervention, selective reporting, whether there was clear reporting without discrepancies, clear eligibility criteria, adequately described interventions, and adequate outcome definition. For all studies, other potential biases or methodological problems of note were also captured. Where methodological issues may have pertained only to some reported outcomes, this was noted.

Risk of bias of diagnostic test studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies-1 (QUADAS 2) tool[1277] with selected questions pertaining to sample selection, blinding, prespecified methods, and completeness of data and analyses. For association studies that evaluated potential predictors of outcomes, risk of bias was assessed based on completeness and appropriateness of sample selection and analyses, definitions of predictors and outcomes, completeness of reporting, and other methodologic and reporting issues, all of which were notated.

Risk of bias for existing systematic reviews was assessed based on the Assessment of Multiple Systematic Reviews 2 (AMSTAR 2) quality assessment tool.[1278] Systematic reviews were consider to be of high quality if at least 2 electronic databases were searched (including either MEDLINE or Embase); there was a clear description of study eligibility criteria, duplicate screening, explicit check of extracted data by another researcher, risk of bias assessment; and appropriate meta-analysis methods were used. Systematic reviews that were of poor quality solely due to poor meta-analysis methods, but were otherwise eligible, were maintained but all pertinent meta-analyses were conducted again.

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All risk of bias assessments were conducted independently by 2 members of the ERT, with disagreements resolved by internal discussion and consultation with a third ERT member, as needed.

Evidence synthesis and meta-analysis

Data for each topic was presented to the Work Group in summary tables describing study characteristics, interventions (or prediction factors), outcomes, results data, summary results, and risk of bias.

Measures of treatment effect – All evaluated outcomes of interventions were dichotomous. Thus, results that were summarized or meta-analyzed by the ERT were expressed as RRs or HRs with 95% CIs. Results summarized by existing systematic reviews were extracted in the metric reported (e.g., OR) and were typically not converted to RRs. Analyses of associations were extracted in the reported metrics, preferentially including the most-adjusted analyses. For diagnostic test studies, the ERT extracted reported measures of test accuracy, including sensitivity and specificity, receiver operating characteristic area under the curve, and likelihood ratios.

Data synthesis - Meta-analysis was conducted if there were 3 or more studies that were sufficiently similar with respect to key variables (population characteristics, study duration, comparisons). The ERT used their judgment to determine sufficient similarities. Meta-analyses were not excluded solely for statistical heterogeneity (differences across studies in effect size estimates). Restricted maximum likelihood (REML) model meta-analyses of the risk ratio for outcomes in Stata were conducted. Where pertinent, the ERT combined existing systematic reviews with additional primary studies using the same approach as *de novo* meta-analysis, using data from all primary studies.

Assessment of heterogeneity – Heterogeneity was assessed by visual inspection of forest plots of standardized mean effect sizes and of RRs, and χ^2 tests. A $P < 0.05$ was used to denote statistical heterogeneity, with an I^2 calculated to measure the proportion of total variation in the estimates of treatment effect that was due to heterogeneity beyond chance.

Grading the certainty of the evidence

The certainty of the evidence related to each critical and important outcome was assessed based on a GRADE approach (Table 64),[1274] which assesses the certainty of the evidence for each outcome, with some modifications. For each outcome, the initial grade for the certainty of evidence started at "high" but was then lowered if there were serious methodological limitations (i.e., risk of bias) across the aggregate of studies, if there were clinically important inconsistencies in the results across studies or large statistically heterogeneity by meta-analysis (unless the direction of effect was consistent), if there was

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uncertainty about the directness of evidence (including limited applicability of the findings to the population of interest), if the outcome measure estimates were imprecise or based on sparse studies, or if there was thought to be a high likelihood of reporting bias. The final grade for the certainty of the evidence for an outcome could be high (A), moderate (B), low (C), or very low (D) (Table 65). If there was a large degree of unexplained inconsistency across studies, very imprecise summary estimates of effect, or only a single small study, the certainty of evidence for the given outcome was rated very low.

In determining the overall certainty of evidence for each comparison of interventions (or diagnostic test), the primary purpose of the intervention was prioritized when assessing across prioritized outcomes. Thus, for interventions to predict or prevent AKI, the overall certainty of evidence was determined first based on the certainty of evidence for incident AKI. However, if the certainty of evidence for mortality or other prioritized AKI-related outcomes was greater than for incident AKI, the overall certainty of evidence was graded per the other prioritized outcomes. Similarly for interventions primarily used to manage AKI, the overall certainty of evidence was first determined based on RRT but was upgraded if the certainty of evidence for death or MAKE were higher than for RRT.

Evidence profiles

Evidence profiles were developed to include a description of the population and the intervention and comparator. In addition, the evidence profiles include risk of bias rating and results from the data synthesis. The grading of the certainty of the evidence for each critical and important outcome is also provided in these tables (Data Supplement Appendixes C and D).

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Table 64 | GRADE system for grading the certainty of evidence

Study design	Step 1—Starting grade for the certainty of the evidence	Step 2—Lower grade	Step 3—Raise grade for observational studies
RCT	High	Study limitations: –1, serious –2, very serious	Strength of association +1, large effect size (e.g., <0.5 or >2) +2, very large effect size (e.g., <0.2 or >5)
	Moderate	Inconsistency: –1, serious –2, very serious	Evidence of a dose–response gradient
Observational	Low	Indirectness: –1, serious –2, very serious	All plausible confounding would reduce the demonstrated effect
	Very low	Imprecision: –1 serious –2 very serious -3 extremely serious Publication bias: –1 strongly suspected	

GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; RCT, randomized controlled trial.

Table 65 | Classification for certainty of evidence

Grade	Certainty of evidence	Meaning
A	High	We are confident that the true effect is close to the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very low	The estimate of effect is very uncertain, and often it will be far from the true effect.

Developing the recommendations

Recommendations from the *KDIGO 2012 Clinical Practice Guideline for Acute Kidney Injury* were considered in the context of new evidence and current standards of care by the Work Group Co-Chairs and Work Group members and updated as appropriate.[608] Practice points were not yet proposed as a separate category in 2012, so the KDIGO 2026 Work Group considered the following options: (i) where new evidence did not suggest a

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change to graded recommendations, the statements were retained as graded recommendations; (ii) graded recommendations were updated, where appropriate, based on new evidence; (iii) existing recommendations that fit the criteria for practice points were rewritten as practice points; and (iv) new guideline statements (both recommendations and practice points) were generated for new clinical questions in the 2026 update.

Grading the strength of the recommendations

The strength of a recommendation was classified by the Work Group as Level 1, "We recommend" or Level 2, "We suggest" (Table 66). The strength of a recommendation was determined by the balance of benefits and harms across all critical and important outcomes, the grading of the overall certainty of the evidence, patient values and preferences, resource use and costs, and considerations for implementation (Table 67).

Table 66 | KDIGO nomenclature and description for grading recommendations

Grade	Implications		
	Patients	**Clinicians**	**Policy**
Level 1, "We recommend"	Most people in your situation would want the recommended course of action, and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2, "We suggest"	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

KDIGO, Kidney Disease: Improving Global Outcomes.

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Table 67 | Determinants of the strength of recommendation

Factors	Comment
Balance of benefits and harms	The larger the difference between the desirable and undesirable effects, the more likely a Level 1 recommendation is provided. The narrower the gradient, the more likely a Level 2 recommendation is provided.
Certainty of evidence	The higher the certainty of the evidence, the more likely a Level 1 recommendation is warranted. However, there are exceptions for which low or very low certainty of the evidence will warrant a Level 1 recommendation.
Values and preferences	The more variability in values and preferences, or the more uncertainty in values and preferences, the more likely a Level 1 recommendation is warranted. Values and preferences were obtained from the literature, when possible, or were assessed by the judgment of the Work Group when robust evidence was not identified.
Resource use and costs	The higher the cost of an intervention—that is, the more resources consumed—the less likely a Level 1 recommendation is warranted.

Balance of benefits and harms - The Work Group determined the anticipated net health benefit on the basis of expected benefits and harms across all critical and important outcomes from the underlying evidence review.

Overall certainty of evidence - The overall certainty of the evidence for each recommendation was determined by the certainty of evidence for all critical and important outcomes, considering the relative importance of each outcome to the population of interest, as described above. For recommendations about diagnostic test studies, where there was evidence only for the diagnostic accuracy of the tests (e.g., to predict AKI) and no evidence from RCTs that implemented the diagnostic tests, the overall certainty of the evidence to support the recommendation was downgraded 1 level due to indirectness of the evidence. In addition, when eligible studies included only adults for a given specific topic, the pediatricians in the Work Group, together with the Co-Chairs and Methods Committee representatives, determined whether there was concern about applicability to children and, where there was, the overall certainty of the evidence to support the recommendation was also downgraded one level due to indirectness. In these instances, the downgrading is explained in each certainty of evidence description. The final grade for the certainty of the evidence for an outcome could be high (A), moderate (B), low (C), or very low (D) (Tables 64 and 65).

Patient values and preferences - The Work Group included 2 people with lived experience of AKI. These members' unique perspectives and lived experience, in addition to the Work Group understanding of patient preferences and priorities, informed decisions about the strength of the recommendations. A systematic review of qualitative studies on patient priorities and preferences was not undertaken for this guideline.

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Resource use and costs - Healthcare and non-healthcare resources, including all inputs in the treatment management pathway, were considered in grading the strength of a recommendation.[468] The following resources were considered: direct healthcare costs, non–healthcare resources (such as transportation and social services), informal caregiver resources (e.g., time of family and caregivers), and changes in productivity. No formal economic evaluations, including cost-effectiveness analysis, were conducted.

Practice points

In addition to graded recommendations, KDIGO guidelines now include practice points to help healthcare professionals better evaluate and implement the guidance from the expert Work Group. Practice points are consensus statements about a specific aspect of care and supplement recommendations. Although systematic reviews are not performed for clinical questions underlying practice points, they are often crafted to help readers implement the guidance from graded recommendations. Practice points represent the expert judgment of the guideline Work Group, and they may be based on limited evidence. Practice points are sometimes formatted as a table, a figure, or an algorithm, to make them easier to use in clinical practice.

Format for guideline recommendations and practice points

Each guideline recommendation provides an assessment of the strength of the recommendation (Level 1, "we recommend" or Level 2, "we suggest") and the overall certainty of the evidence (high [A], moderate [B], low [C], very low [D]). The recommendation statements are followed by Key information (Balance of benefits and harms, Certainty of the evidence, Values and preferences, Resource use and costs, Considerations for implementation) and Rationale. Each recommendation is linked to a relevant evidence profile. An underlying rationale may also support a practice point.

Limitations of the guideline development process

Although the literature searches were intended to be comprehensive, they were not exhaustive. MEDLINE and Embase databases were searched, but other specialty or regional databases were not. Hand searches of journals were not performed, and review articles and textbook chapters were not systematically searched; however, existing systematic review and clinical practice guidelines were hand-searched. In addition, any important studies known to domain experts that were missed by the electronic literature searches were added to retrieved articles and reviewed by the Work Group for eligibility.

The ERT did not systematically review all topics of interventions that are amenable to trials. Topics were prioritized by the Work Group. Other topics were addressed by practice points. Almost all research questions pertaining to interventions were restricted to RCTs. Other study designs that may inform the guideline were not systematically

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reviewed. We did not review qualitative research studies (e.g., focus groups) to inform determinations about values and preferences, or cost-effectiveness analyses to inform determinations about resource use or costs.

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